Fall 1985

PART I PREPARATION OF NOVEL LACTONES AND THEIR PRECURSORS DERIVED FROM METHYL SALICYLATE PART II NUCLEOPHILIC AROMATIC SUBSTITUTION IN A DINITROSALICYLIC LACTONE WITH RING OPENING AND ELIMINATION VIA MEISENHEIMER INTERMEDIATES

SCOTT DANIEL ROTHENBERGER
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BY

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BS Albright College, 1981

A DISSERTATION

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in

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September, 1985

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Edward K. Tillinghast, Professor of
Zoology

June 7, 1985

June 7, 1985

I DEDICATE THIS DISSERTATION TO MY WIFE VICKI

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PART II. NUCLEOPHILIC AROMATIC SUBSTITUTION IN A DINITROSALICYLIC LACTONE WITH RING OPENING AND ELIMINATION VIA MEISENHEIMER INTERMEDIATES

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Scott D. Rothenberger
University of New Hampshire, September 1985

Part I

The synthesis, characterization, and physical properties of novel lactones and their precursors derived from methyl salicylate are described. The influence of substituents on the aromatic nucleus in affecting ring closure reactions was examined. Experimental results show that ring closure is enhanced when nitro groups are incorporated in the aromatic ring. Investigations were conducted in the preparation of compounds designed to exhibit ring-chain tautomerism.

Part II

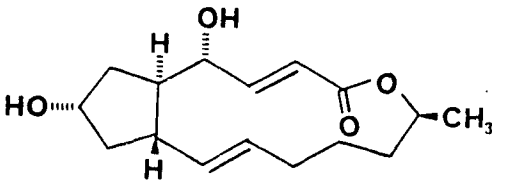
Nucleophilic aromatic substitution reactions were carried out on 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester and the corresponding seven-membered lactone. Nucleophiles chosen for study included iodide, several amines, hydroxide, methoxide, thiophenoxide, thiosulfate, sulfides, thiocyanate, cyanide, and several enolates. Reaction with a nucleophile was accompanied by the consistent loss of the β-hydroxyethoxy unit. In several of these experiments, the isolation and characterization of Meisenheimer complexes was possible. The Meisenheimer intermediates, in turn, could be converted to aromatic products by means of various nucleophiles.

PART I. PREPARATION OF NOVEL LACTONES AND THEIR PRECURSORS DERIVED FROM METHYL SALICYLATE

INTRODUCTION

Macrocyclic compounds occur frequently in nature, at least a thousand of them being antibiotic agents. Among several subgroups of the macrocycles is included the macrocyclic lactones. These compounds generally contain 8-40 membered lactone rings. One or more lactone functionalities may be incorporated within the macro ring, along with other functional groups. These compounds may also have one or more aromatic or nonaromatic rings fused to the macrolactone. Antibacterial, antifungal, cytotoxic and cation-selective properties are often exhibited by the macrocyclic lactones.[1]

A survey of the current literature shows that there has been considerable interest in the preparation of macrocyclic lactones.[2-5] These may contain many chiral centers and a variety of functionality. This is exemplified by brefeldin A (1), a 13-membered lactone fused to a cyclopentane and containing five chiral centers and two trans double bonds.



1

Macrocyclic lactones may contain not only ester groups but also ether linkages, as are often found in naturally occurring macrocyclic ionophores. Nonactin is an example of an ionophoric macrolide with four furan units. The incorporation of these furan ether units into a 32-membered ring forms a hydrophilic cavity capable of transporting ions in biological systems.[6-8]

Polyoxygenated materials have been incorporated into recent syntheses in an effort to mimic properties exhibited by the naturally occurring ionophoric antibiotics.[9-12] Most of the macrocyclic polyether lactones have been synthesized by the now classic ring formation reactions where dibasic acid derivatives are treated with glycols or $\alpha,\omega-$ dihalo compounds.[13-17]

It is known that cyclization to large rings is generally facilitated by the incorporation of heteroatoms.[18] Substituents may play a role in ring formation. An example is illustrated in Figure 1. Experimentally, it was shown that the IR spectrum of solid 2-(2-hydroxyethoxy)-3,5-dichlorobenzaldehyde (KBr pellet) contained no carbonyl band, whereas a solution IR spectrum (THF) did show the presence of a carbonyl. This phenomenon was attributed to the ring tautomer being favored in the solid state.[19] This ring tautomerism can be attributed to the steric bulk of the chlorine on the aromatic nucleus which is somewhat relieved by cyclization. This use of steric bulk on an aromatic

Ring-chain Tautomerism of

2-(2-Hydroxyethoxy)-3,5-dichlorobenzaldehyde

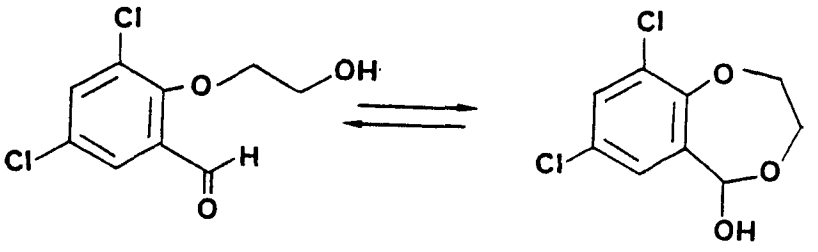


Fig. 1

nucleus in order to favor a ring closure has been alluded to in other literature citations.[20-21] Of interest to this work are the 13 known naturally occurring macrocyclic lactones containing an ortho-fused aromatic nucleus. Most macrocyclic lactones are either nonaromatic or have meta or para substituted aromatic nuclei.[22-24]

Curvularin is the only member in this family devoid of biological activity and which is not a benzoate derivative but rather a phenylactate.[1, 25-27] The remaining members of this family all have two structural features in common: they contain a benzoate lactone and a chiral center at the α' position of the lactone. A general structure is depicted in Figure 2.

Previous work in this laboratory was directed towards the preparation of synthetic analogs of curvularin.[28-29] From readily obtainable salicylic acid and thiosalicylic

General Structure of a Benzoate Lactone

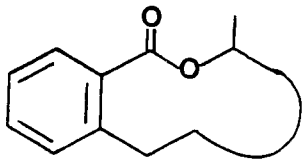


Fig. 2

acid, several acyclic precursors to the lactones were prepared. Some of the acyclic thio ether compounds exhibited an inhibitory effect on the growth of Bacillus subtilis.[30] Therefore, further investigation into acyclic and cyclic ortho-fused benzoates appeared to be warranted.

The goal of this project was the synthesis and examination of a series of ethereal lactones and their acyclic precursors containing an ortho-fused benzene ring. The key starting materials would have the general structure (x= 1-4) in which the functional groups could be modified so as to enhance lactonization (Fig. 3).

The effect of the heteroatom(s) and/or substituents placed on the aromatic nucleus in the facilitation of ring closure could then be studied. After the preparation of such compounds, biological testing could be performed and a comparison drawn with respect to known synthetic ionophoric macrocyles.

General Structure of Polyoxybenzoates

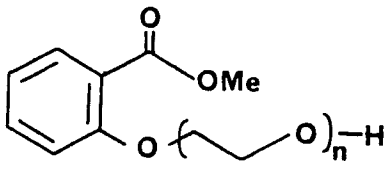


Fig. 3

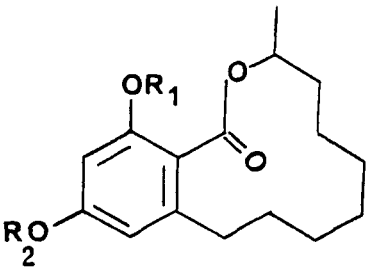
HISTORICAL

There are few metabolites that occur in nature that possess a macrocyclic lactone ring which is ortho-fused to an aromatic nucleus.[25, 31, 32] Prior to 1977, the only known naturally occurring ortho-fused macrocyclic lactones were lasiodiplodin (2), de-O-methyl-lasiodiplodin (3),[33] radicicol (4),[34-36] zearalenone (5),[37-40] curvularin (6)[41-43] and α,β -dehydrocurvularin (7).[44]

The isolation, characterization, and biological activity of these compounds and the early syntheses of curvularin and zearalenone have been reviewed by Malmberg and Linek.[28, 29] This survey will include the more recent isolations and syntheses of the remaining members of the ortho-fused macrocyclic lactones.

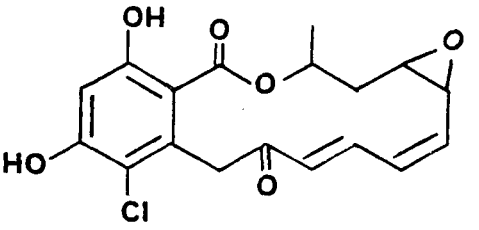
In 1977 Lovell and coworkers isolated and characterized four new zearalenone-related macrolides.[45] The extracts from the fermentation products of Lederle culture LL-Z-1640 showed an inhibition in the growth and mobility of the protozoan Tetrahymena pyriformis. The unidentified fungus yielded four zearalenone-related metabolites, which were assigned numbers LL-Z1640-1,2,3,4 (8, 9, 10, 11). These macrolides were characterized by UV, ^{1}H NMR, IR and MS. Further characterization was carried out by degradative studies and an X-ray crystal

structure on the di-p-chlorobenzoyl derivative of LL-Z1640-1, (8), which proved to be (4'S, 5'S, 10'S)-4',5'-dihydroxy-zearalenone 4-methyl ether. To date, syntheses of these zearalenone metabolites have not been reported.[45]



2 $R_1 = CH_3$ $R_2 = H$

3 $R_1 = H$ $R_2 = H$



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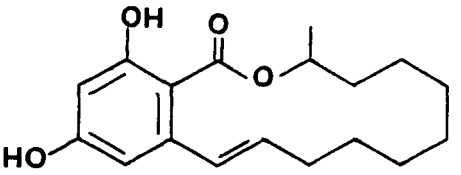

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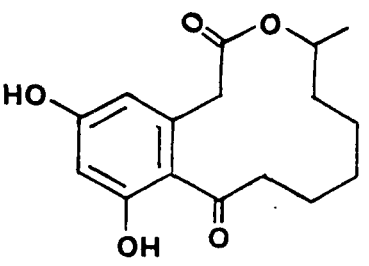

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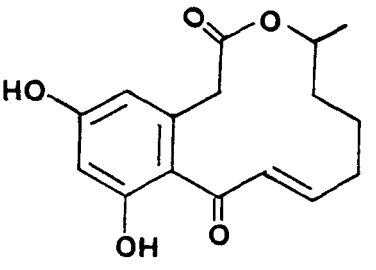

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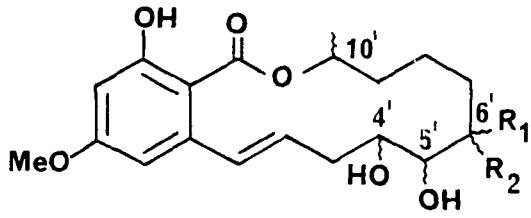
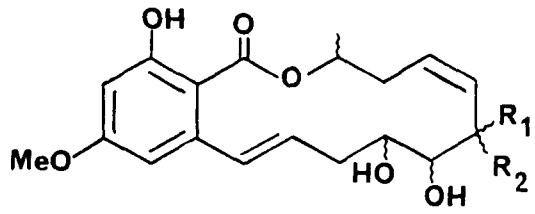


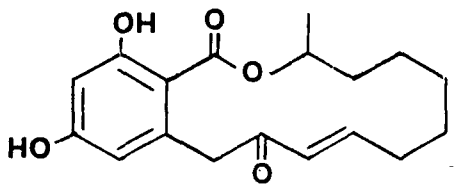
8 $R_1 = R_2 = O$

10 $R_1 = H, R_2 = OH$



9 $R_1 = R_2 = O$

11 $R_1 = H, R_2 = OH$



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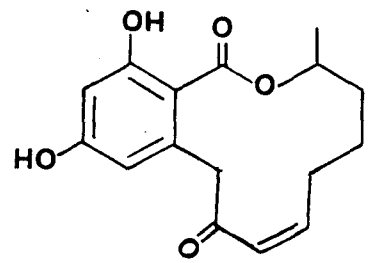

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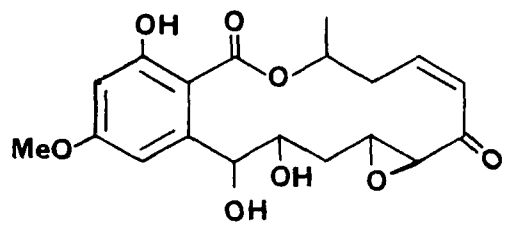


14

In 1978 Oyama and coworkers, in their search for new plant growth inhibitors, isolated two new active compounds which were named trans- (12) and cis-resorcylide (13).

These two compounds were isolated from the ethyl acetate extracts from an unidentified species of Penicillium. The structures of these two compounds were established by means of IR, ^{1}H NMR, UV, and MS information, as well as degradative studies. It was found that the trans-resorcylide was the more biologically active compound, causing an inhibition in the root elongation of Chinese cabbage, lettuce, and rice in seedling tests.[46]

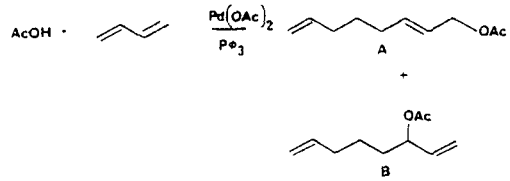
In 1980 another new antibiotic metabolite, hypothemycin (14), was isolated by Nair and Carey from a strain of Hypomyces trichlothecoides.[47] This compound was found to be active against Tetrahymena furgasoni at concentrations of 30 ppm (LD_{100}) and 1 ppm (LD_{50}) and moderately active against Ustilago mayids. Structural characterization of 14 was accomplished from UV, MS, IR, ^{1}H NMR, and ^{13}C NMR spectral data, along with chemical degradation studies. To date there has been no synthesis of this zearalenone-related metabolite reported in the literature.

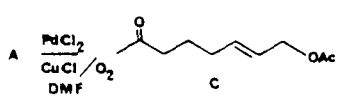
A careful reexamination of lasiodiplodin (2) in 1982 by Lee and coworkers revealed that it exhibited a marked antileukemic activity.[48] The chloroform extracts from Euphorbia splendens containing lasiodiplodin showed significant in vivo inhibitory activity against the growth of P-388 lymphocytic leukemia in the BDF male mouse. This is the first instance in which a member of this family of

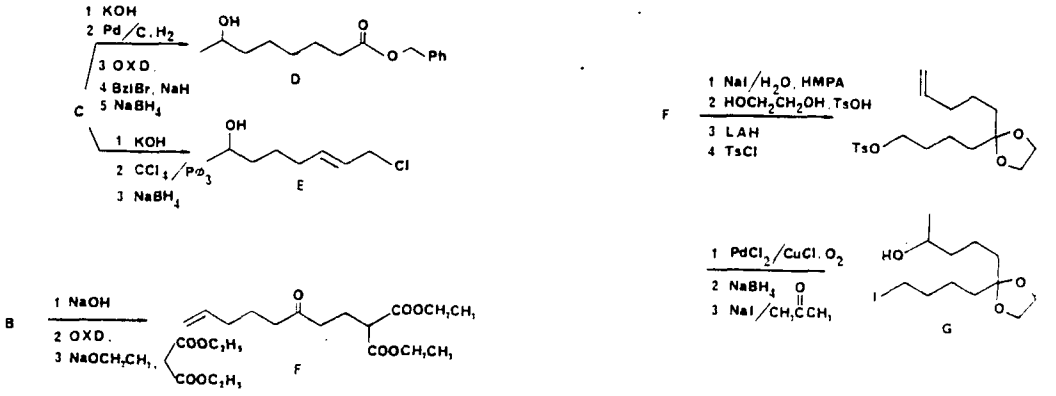
compounds has been shown to exhibit this type of activity.

Two syntheses of zearalenone (5) were reported in the literature about 15 years ago.[38, 44] In these syntheses, the double bond was introduced *via* a Wittig reaction, which did not afford the necessary *trans* double bond selectively. Furthermore, the overall yields after lactonization were very low, 31% and 8% respectively.

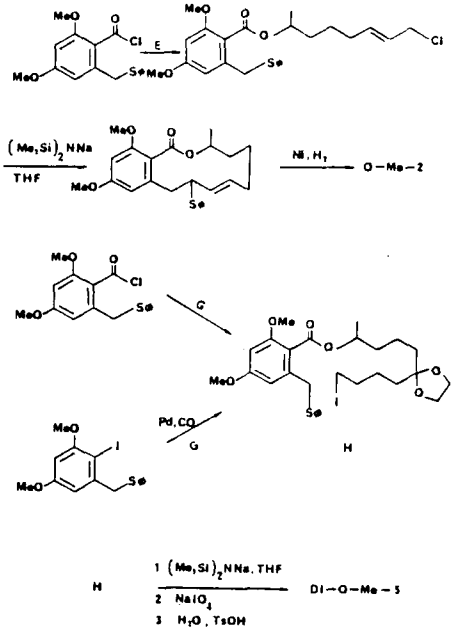
Tsuji and coworkers have developed several methodologies for the synthesis of macrolides. These include palladium-catalyzed carbonylation reactions, anion and dianion cyclizations, and the use of butadiene telomerization as a synthetically useful means of carbon-carbon bond lengthening.[50-53] Making use of these synthetic methods, Tsuji was able to synthesize curvularin (6), zearalenone (5), lasiodiplodin (2), and the *cis*- and *trans*-resorcylides (12, 13). The following synthetic sequences outline the functionalization of butadiene units necessary for the synthesis of these macrolides. These intermediates, derived from telomerized butadiene units, were designed for condensation reactions. This will be demonstrated in the following synthetic schemes.



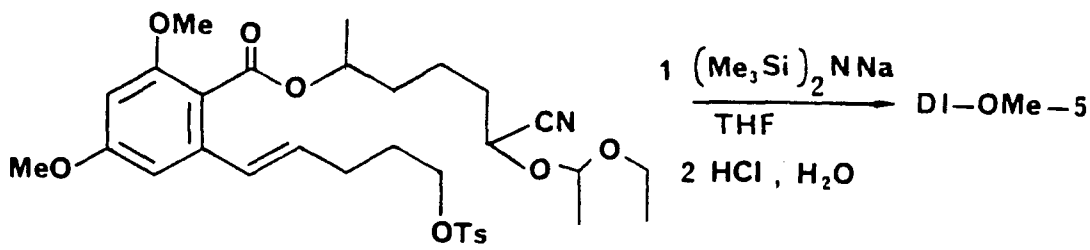




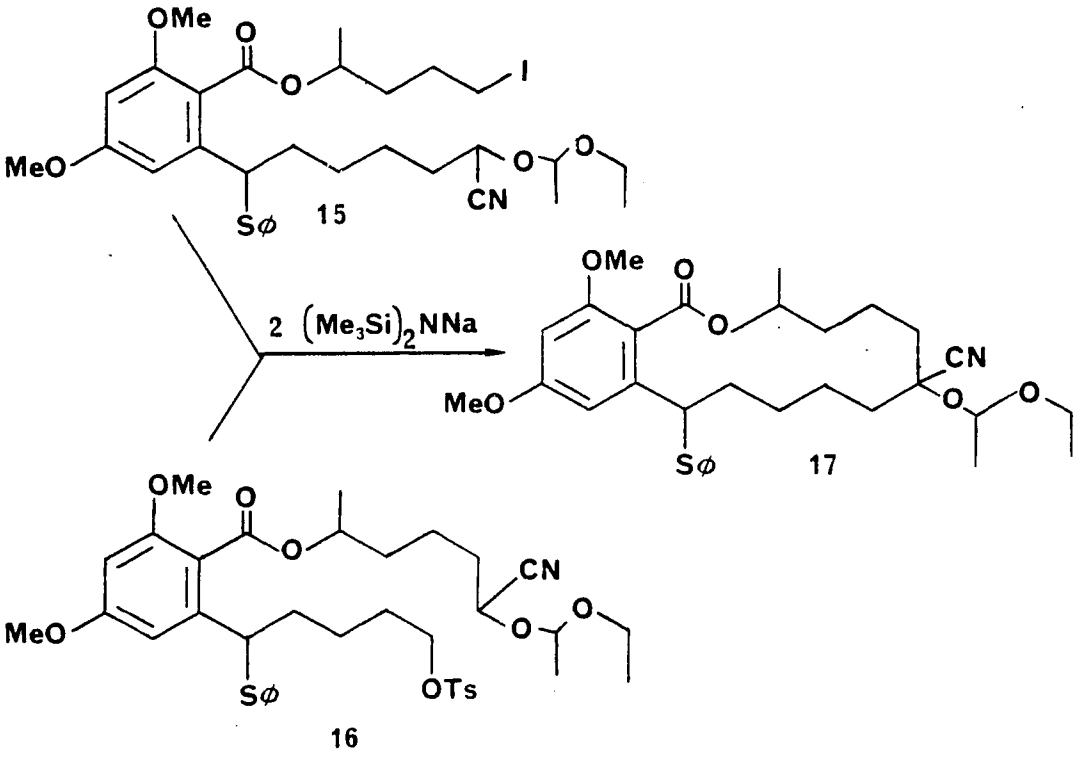
Tsuji and coworkers had previously developed a method of ring cyclization by the intramolecular alkylation of ω-haloalkyl-2-phenylthiomethylbenzoates.[50, 54] This method avoided the usual problems of ring closure by intramolecular esterification of ω-hydroxyacids.[55-58] The phenylthio group can be removed by reduction or oxidized if necessary. The use of the phenylthio group in conjunction with the previously synthesized butadiene units is demonstrated in the following synthetic schemes for O-methyl-2 and di-O-methyl-5.[50, 51, 54]



Tsuji and coworkers had previously investigated the applicability of using protected cyanohydrins in ring closure reactions. By this methodology, a protected cyanohydrin was used as an effective intermediate for ring closure in the synthesis of di-O-methyl-5.[59]

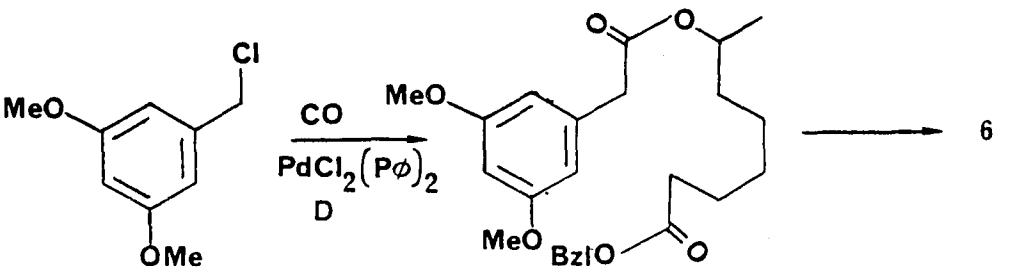


Tsuji and coworkers have more recently combined the methodologies of the protected cyanohydrin and the phenylthiomethyl group in the preparation of di-O-methyl-5. Addition of one equivalent of base to 15 or 16 forms the benzylic anion. When a second equivalent of base is added, an anion is formed at the site of the protected cyanohydrin. Intramolecular alkylation of the cyanohydrin anion was found to occur readily. Intermolecular reactions were minimized because of the presence of two negative charges in the same molecule. High dilution techniques were not needed when this method of preparation was used in the synthesis of 17, an intermediate in the pathway to di-O-methyl-5.[60]



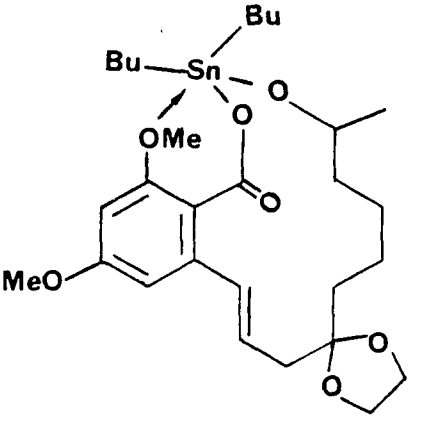
$$17 \xrightarrow[2\ NaIO_4]{1\ HCl,\ H_2O} DI-OMe-5$$

In the work of Tsuji and coworkers, palladium-catalyzed carbonylation was used effectively in the presence of a telomerized butadiene unit D to afford 18, a precursor to curvularin.[61] The conversion of the benzyl ester 18 to the di-O-methyl-6 had already been accomplished.[62]



18

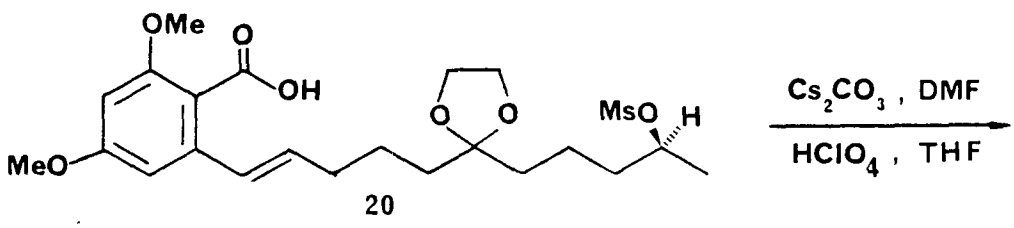
In recent years metal-assisted template effects have become of interest as synthetic methods for macrolide ring closures. Steliou and coworkers attempted a synthesis of zearalenone (5), using catalytic amounts of di-n-butyltin oxide to cyclize a seco-hydroxy acid. Their failure was attributed to chelation effects, where a six-membered cyclic intermediate about the tin atom restricts conformational freedom, such that the loss of tin oxide is unfavorable in 19.[63, 64]

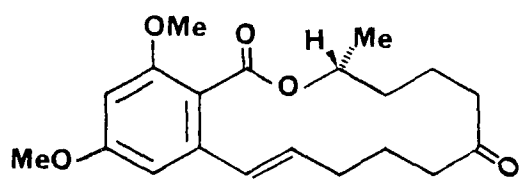


19

Kellogg and Kruizinga approached the synthesis of (R)-zearalenone, (5), by using the cesium ion as the metal template in lactonization of a carboxylate. Previous studies by Kellogg had shown a favored effect in the synthesis of large macrocyclic polyethers when the cesium ion was employed as a metal template.[65-67] This method of ring closure was extended to an aliphatic polymethylene chain in the synthesis of (R)-zearalenone (5).[68]

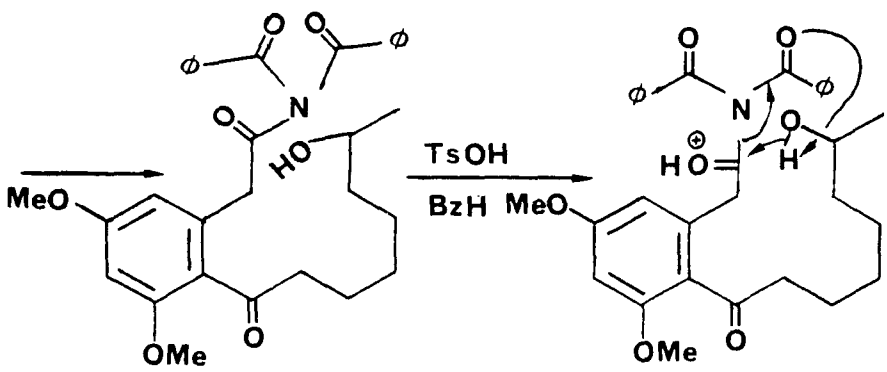
Naturally occurring (S)-zearalenone (5) was converted into 20 by the known procedure.[69] Treatment of 20 with cesium carbonate in DMF followed by hydrolysis of the ketal afforded the R enantiomer of di-O-methyl-5 in 80% yield.





DI—OMe—5

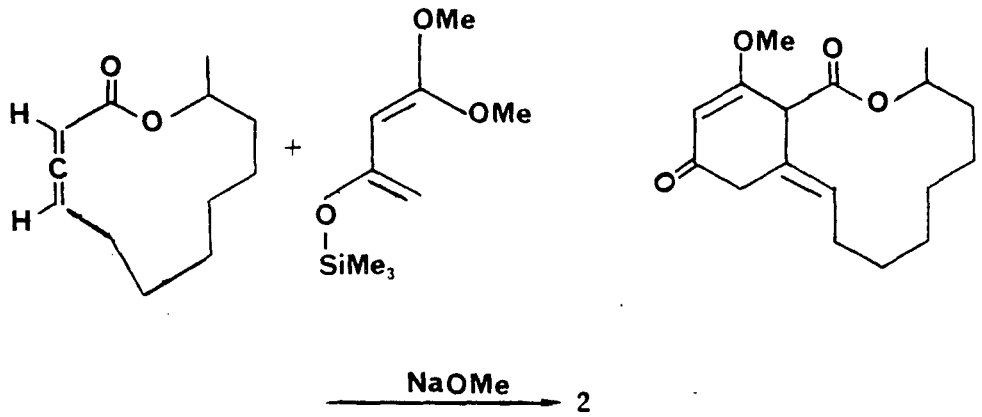
A new method of ring closure where oxazoles function as masked carboxylates has been developed by Wasserman and coworkers.[70, 71] Using this approach, Wasserman was able to synthesize (±)-di-O-methyl-6.[72] The intramolecular cyclization under acid catalysis and high dilution conditions involves the activated triamide derived from the corresponding oxazole.



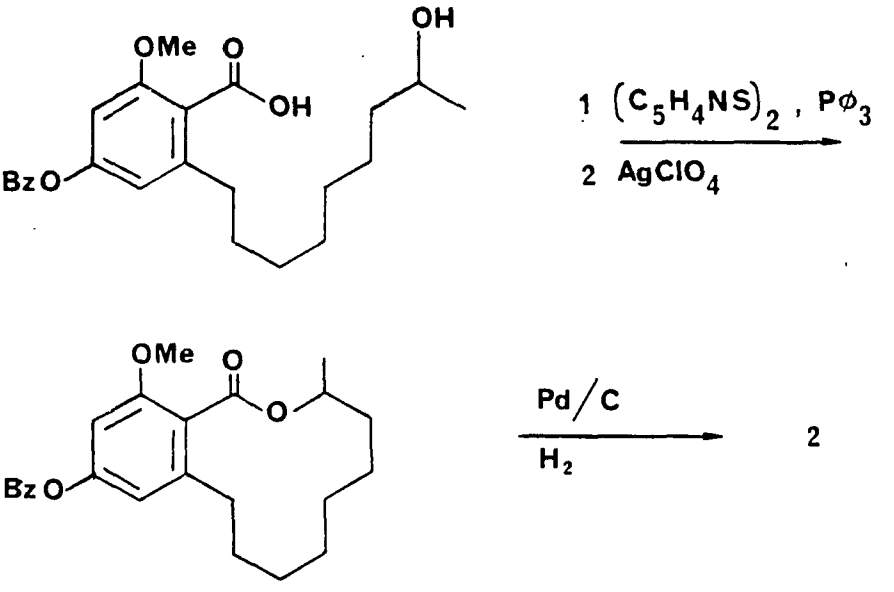
DI—OMe—6

Gerlach and coworkers have synthesized lasiodiplodin (2) by two methods. In their first route lactonization as the final step of the synthesis was avoided by using a chiral allene as the macrocyclic substrate. The allene was allowed to react with 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene in a Diels-Alder cyclization leading to a precursor of the aromatic moiety.

Aromatization was effected by treatment of the keto ether with a solution of sodium methoxide to afford (±) lasiodiplodin (2).[73]



Gerlach prepared racemic lasiodiplodin by silver perchlorate-mediated lactonization, a method previously developed in his laboratory.[74, 75] The ω-hydroxyacid was first synthesized. This was then treated with di-2-pyridyl disulfide in the presence of triphenylphosphine. The resulting activated intermediate was treated with silver perchlorate to effect lactonization. After catalytic removal of the benzyl group, racemic lasiodiplodin (2) was obtained in 68% yield.



Because the crucial synthetic step in the preparation of macrocyclic lactones has generally been the lactonization step, there has continued to be great interest in methods to achieve lactone formation. Various means of preparation of macrocyclic lactones have been developed and have been reported previously by Malmberg and Linek or have been described in reviews.[2-5, 28, 29, 77-79] This survey will continue from these points of reference. Throughout the preceding part of this dissertation, several of these methods of lactonization have already been presented. What follows is a survey of recent applications of established methods or new

lactonization methods reported since the reviews by Malmberg and Linek.

Macrocyclic lactones have been synthesized by ring forming reactions where dibasic acid derivatives are treated with α,ω — dihalo compounds.[3, 9, 80] In a recent synthesis, Samat and coworkers prepared a simple model for the nactin antibiotic series by making use of this approach (Fig. 4).[81]

Synthesis of Nactin

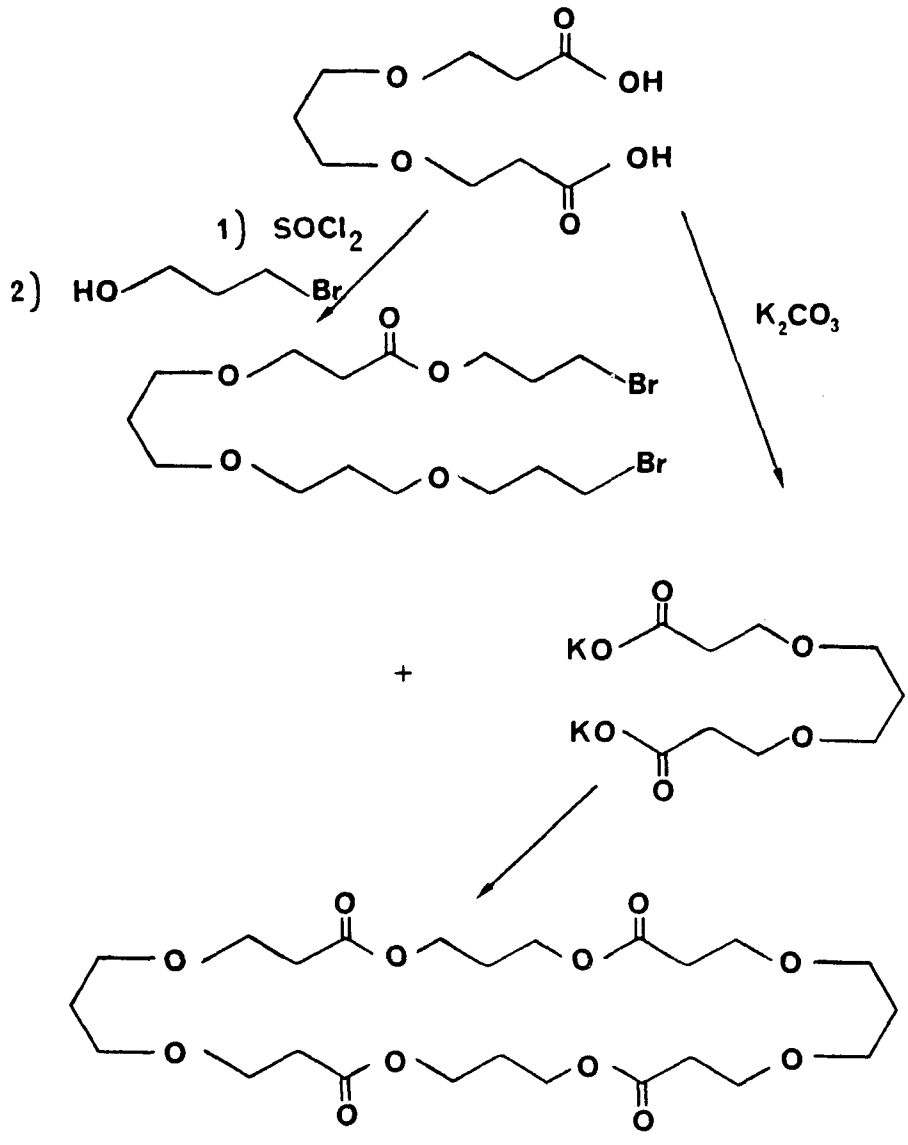


Fig. 4

The use of cyclic tin polyethers as reagents in the preparation of macrocyclic polyether esters has been studied by Shanzer and coworkers. It was found that cyclic distannoxanes, when treated with diacid chlorides, gave macrocyclic polyether tetraesters in good yield, as outlined below (Fig. 5).[82-87]

Cyclic Distannoxanes

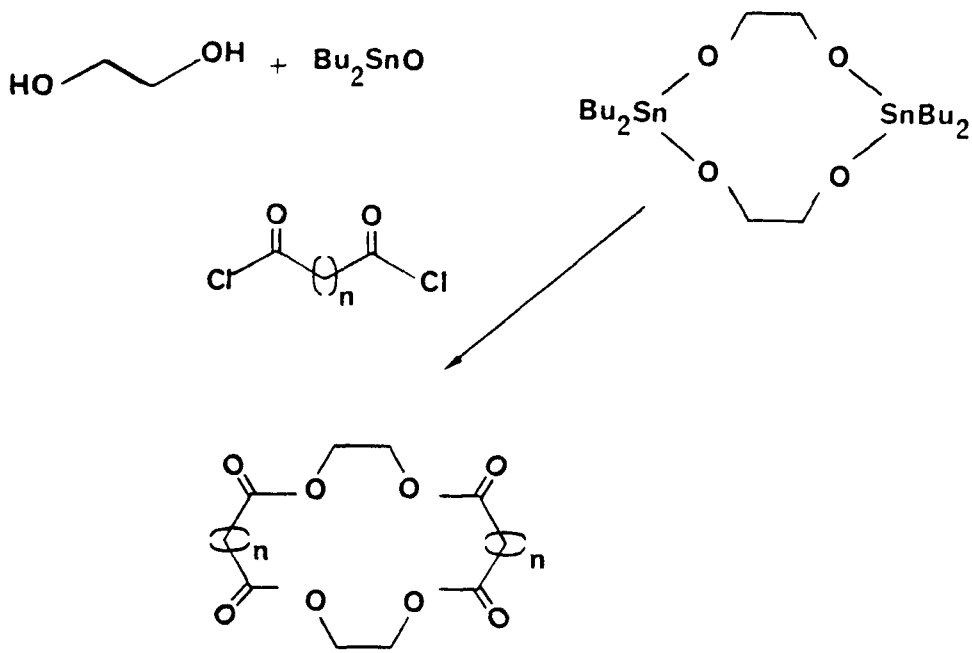


Fig. 5

Tisnes and coworkers have also developed a method of tin template cyclization using linear alkoxytin complexes. The linear alkoxytin complex is treated with diacid fluorides to form macrocyclic polyether esters.

Preliminary results have shown great promise in this area of chemistry (Fig. 6).[88]

Condensation of Acid Fluorides with Linear Alkoxytin Complexes

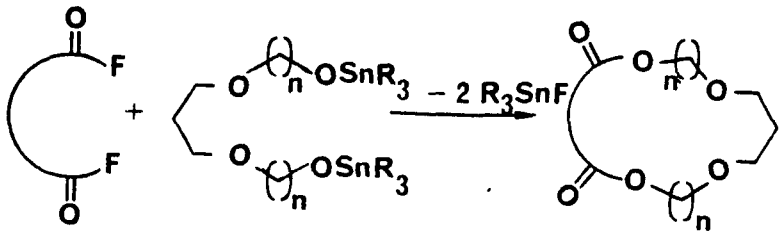
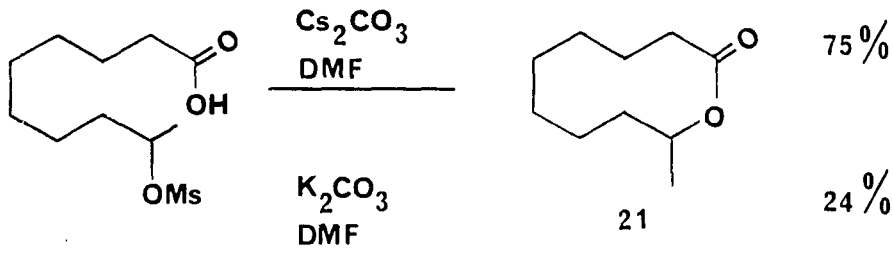


Fig. 6

While the use of tin templates has been shown to be an effective means for ring closure in macrocyclization, this template effect is not unique to tin reagents. As previously shown, cesium, silver, and other metal cations appear to play an important role in some ring cyclizations. Barbier demonstrated that in the synthesis of phoracantholid I (21), the choice of the metal ion was a factor in lactonization. When the protected seco-acid was treated with cesium carbonate, an isolated yield of 75% of 21 was obtained. When an analogous reaction was performed with potassium carbonate, the isolated yield of 21 decreased to 25%.[89]



Rastetter and Phillon have developed new synthetic methods for template driven macrolide ring closures.[90, 91] ω -Hydroxy thioesters are cyclized by mixing the performed thioester with potassium tert-butoxide in aprotic solvents such as benzene and THF. High to medium dilution conditions were employed which resulted in the formation of macrocyclic lactones with ring sizes of 11, 12, and 15 in approximately 70% yields (Fig. 7).

A more common approach toward macrocyclic ring lactonization has been the use of activated carboxylic acids. Corey and Mukiyama have developed a series of these activating compounds using pyridyl disulfide substrates. This area of chemistry was reviewed by Linek.[29] Since that time, additional work has been performed where the 2,2'-dipyridyl disulfides were activating agents.[92-96] In a study of the relative rates of lactonization of ω -hydroxy-n-alkanoic acids (ring

size = 12-21), it was found that formation of the 16-membered ring was fastest.[92]

Sulfur Template Thioesters used in the Formation of Lactones

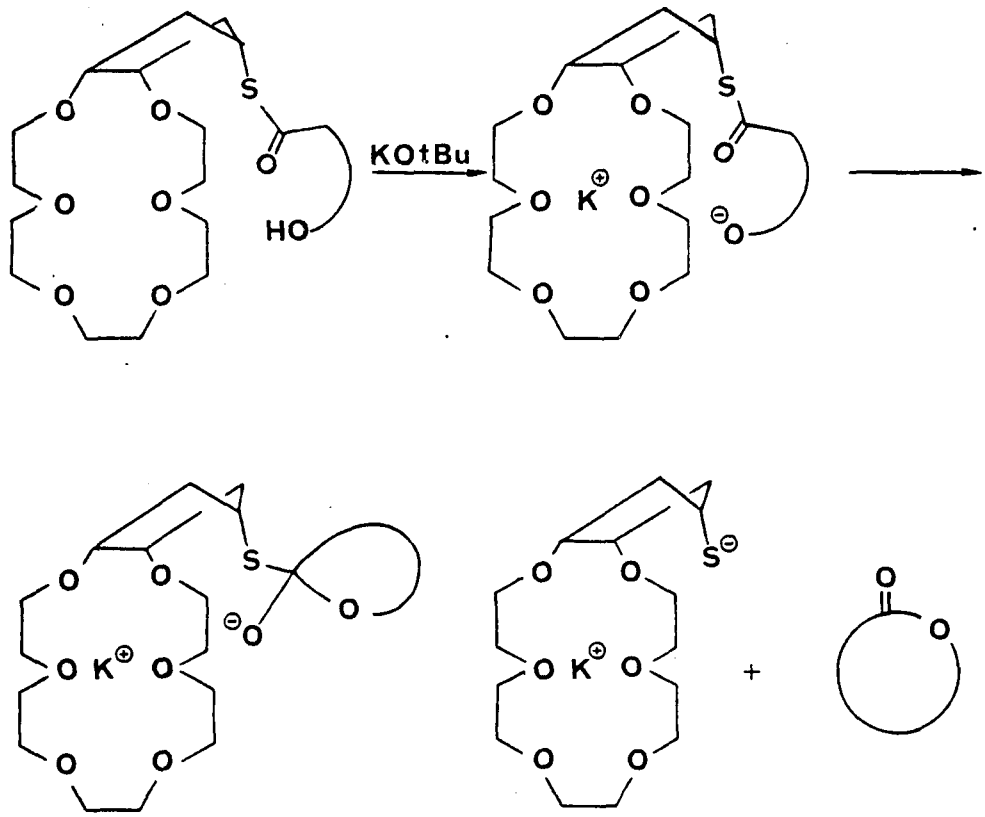


Fig. 7

A variation in the preparation of an activated ω-hydroxy-carboxylic acid derivative is outlined in the following reaction sequence. Vorkuggen found that when ω-hydroxyacids are treated with N,N-dimethylformamide dineopentylacetal in toluene, lactonization occurs.[97] It

is postulated that ring closure is facilitated by the activated dipolar intermediate 22 (Fig. 8).

N,N-Dimethylformamide Dineopentylacetal Activation for Lactonization

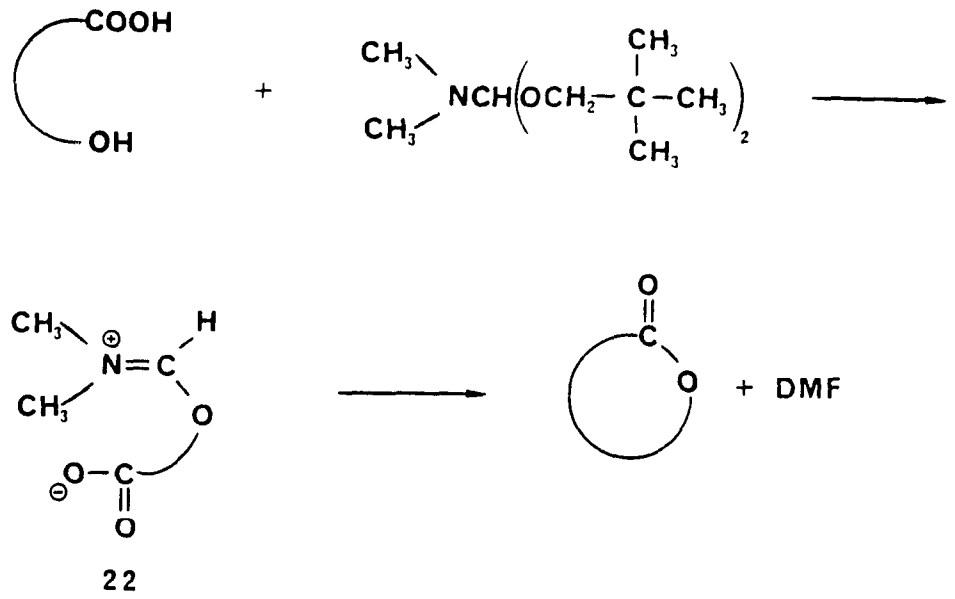


Fig. 8

Schmidt and Dietsche have been successful in preparing 16-20 membered lactones in greater than 90% yields when an ω-hydroxyacid is treated with the thioimide 23.[98] The thioimide is first prepared from 1-phenyl-2-tetrazoline-5-thione and t-butyl isocyanate. Reaction conditions are mild and carried out at substrate concentrations of 3.5×10^{-3} M. The following example (Fig. 9) illustrates the method.

A versatile method of ring closure has been developed by Mitsunobu and coworkers.[99-100] The reagent diethyl azodicarboxylate (DEAD) when used in the presence of triphenylphosphine becomes a powerful activating agent for a wide variety of nucleophiles. An ω-hydroxyacid can be lactonized in generally high yields when treated with DEAD

Thioimide Activation of ω-Hydroxy-Carboxylic Acids

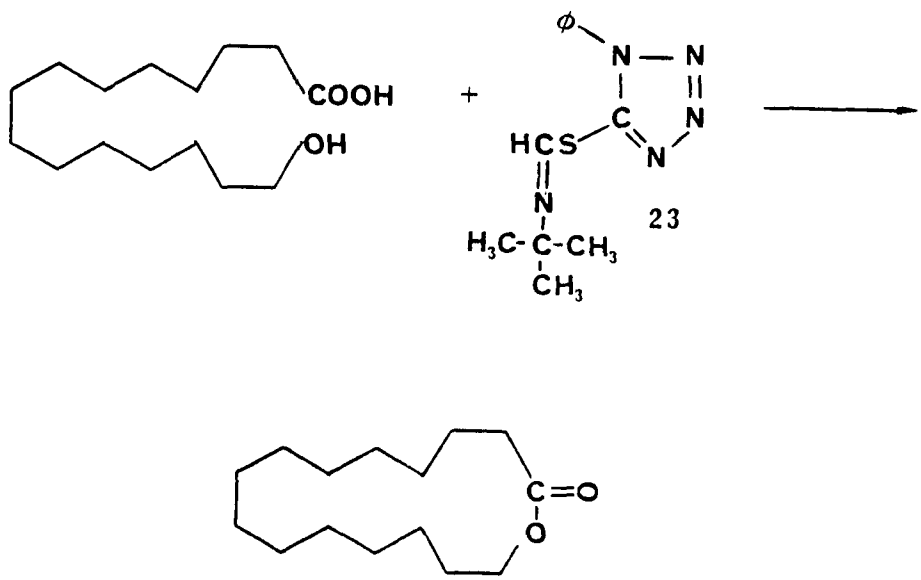
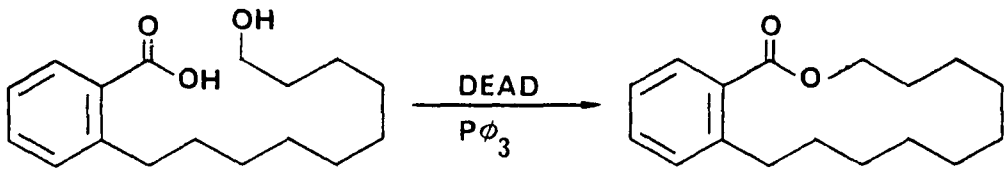


Fig. 9

and triphenylphosphine. Gerlach and Seebach have used the "Mitsunobu" reaction in the lactonization step in the synthesis of the macrolides pyrenophorin and vermiculin.[101, 102] An example is shown where the ω-

hydroxyacid was treated under "Mitsunobu" conditions to afford dideoxyzearalane (23).



An elegant triphase catalytic method of lactonization has been developed by Regen and Kimura.[103] A mesylated ω-hydroxyacid is added to a suspension of toluene/aqueous potassium bicarbonate and phosphonium mesylate resin. This triphase mixture is stirred at room temperature; workup of the organic layer provides the lactonized product. In this manner 7-14 membered lactones have been prepared in up to 80% yield. A schematic diagram shows how this lactonization may occur (Fig. 10). An acid-base reaction between the resin and the carboxylic acid would appear to occur which is then followed by ion exchange. The carboxylate may then effect an intraresin nucleophilic displacement of the mesylate. This affords the mesylated resin and lactone, which is transferred to the organic phase.

Triphase Lactonization

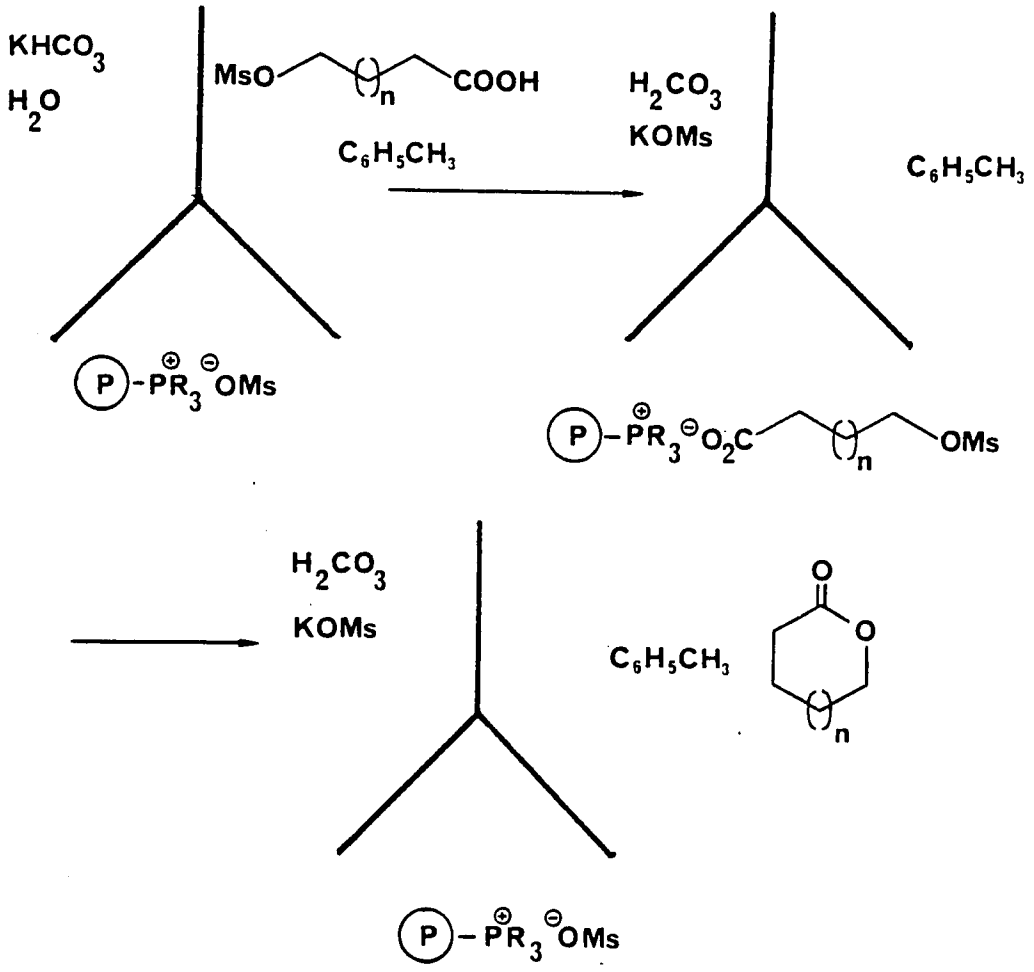


Fig. 10

EXPERIMENTAL

All temperatures reported throughout this text are in degrees Celsius. Melting points were determined with a Thomas Hoover Model 6406-H melting point apparatus.

All elemental analyses were performed by Mr. James Gould and Ms. Deanna Cardin at the University of New Hampshire, except for one sample done by Galbraith Laboratories, Inc., Knoxville, Tennessee. The analyses done at the University of New Hampshire were performed on either a Perkin-Elmer 240B elemental analyzer or an F and M 185 carbon, hydrogen, and nitrogen analyzer.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 283 D grating spectrophotometer and are reported in cm^{-1}. All solid samples were prepared as KBr pellets and all liquids were analyzed as neat samples between NaCl plates. ^{1}H NMR spectra were determined on either a JEOL FX 90Q FTNMR at 90 MHz or a Varian EM360A operating at 60 MHz. ^{13}C NMR spectra were recorded on a JEOL FX 90Q FTNMR operating at 22.5 MHz. The spectra, measured relative to tetramethyl silane as the internal standard, are reported in parts per million (ppm) from TMS. The multiplicity and intensity of each signal are described wherever possible. Ultraviolet and visible spectra (UV-VIS) were recorded on a Varian/Cary 219 spectrophotometer interfaced with an

Apple-IIe computer to record spectra. All wavelengths were recorded in nanometers (nm) and the molar absorptivities calculated from absorbances.

Mass spectra (MS) were obtained from a Hitachi Perkin-Elmer Model RMU-6E by Mr. William Dotchin, University of New Hampshire Instrumentation Center. The molecular ion, if present, and major fragments are recorded with their relative intensities.

Numbered IR, UV, and NMR spectra are on file in the Department of Chemistry, University of New Hampshire.

Thin layer chromatography (TLC) was accomplished with Baker-Flex Silica Gel IB-F on Mylar plates that were dried in an oven prior to use. All spots were visualized under a short wavelength (254nm) UV lamp. Preparative TLC plates were prepared on 20 x 20 cm glass plates with EM Reagent Silica Gel 60 PF-254 which contained $CaSO_4$. Flash chromatography was performed in a 38-mm diameter column packed with 6" of EM Reagent Kieselgel 60, 230-400 mesh ASTM or Baker TLC Reagent, Silica Gel 7. Aluminum oxide EM Reagent, neutral 70-230 mesh ASTM, was used for lactonization experiments.

High pressure liquid chromatography (HPLC) was carried out with a Waters Associates Prep LC/System 500 through one PrepPak-500/Silica column (normal phase). The solvent system was either ethyl acetate/hexane or acetone in the ratios reported. HPLC grade solvents were

purchased from VWR Scientific Company and used without further purification.

Solvents were obtained from the University of New Hampshire stockroom. Acetonitrile was dried over calcium chloride and distilled from phosphorus pentoxide; methylene chloride was dried over calcium hydride, distilled, and stored over 3A molecular sieves; dimethyl sulfoxide (DMSO) was dried over calcium hydride and distilled; pyridine (Aldrich Chemical Company) was dried and distilled from sodium hydroxide; chloroform was dried and distilled from calcium chloride; tetrahydrofuran (THF) was distilled from benzophenone ketyl; hexane was distilled from calcium hydride; toluene was stored over sodium wire; aniline was dried and distilled from sodium hydroxide; and triethylamine was dried and distilled from sodium hydroxide.

Chemicals were purchased from Aldrich, VWR, or Lancaster Chemical companies and used without further purification.

Mobay Chemical Company supplied 2-(2-hydroxyethoxy)-benzoic acid, methyl ester (26) and 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid, methyl ester (27).

Purification of 2-(2-Hydroxyethoxy)-benzoic Acid, Methyl Ester.

A. Flash Chromatography

A 24" x 1-1/2" flash chromatography column was prepared by the method described by Still.[111] A glass wool plug was first inserted into the column followed by 1/4" of sand, 9" of dry silica gel (230-400 mesh Kieselgel 60), and then 1/4" of sand. The column was wetted with diethyl ether and the silica gel was compacted to a column height of 6" under pressure (Compressed air). A solution of 3.0 g of crude 2-(2-hydroxyethoxy)-benzoic acid, methyl ester in 10 mL of diethyl ether was placed on the column head and eluted with 420 mL of diethyl ether at a flow rate of 2"/min. The liquid was collected in 20 x 20 mL fractions, with the first 80 mL discarded as forerun. TLC analysis showed a good separation of 3 components at R_f values of 0.87 (dilactone), 0.46 2-(2-hydroxyethoxy)-benzoic acid, methyl ester, and 0.10 (baseline tar). Fractions 1-5 with R_f values of 0.87 were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.2 g (7%) recovery of dilactone: mp 164-165°; IR (4782) 3100 (aromatic C-H stretching), 1730, 1710 (ester C=O), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend), 750 (o-substitution); ^1H NMR (6268) (acetone) 7.6-6.9 (m, 8, aromatics), 4.7-4.2 (m, 8, 2 OCH_2CH_2O); ^{13}C NMR

(3294) ($CDCl_3$) 168.10, 157.18, 133.11, 131.29, 121.43, 120.69, 112.24, 65.58, 63.27; MS (529) 328 (24), 191 (63), 164 (60), 120 (100), 92 (58).

Anal. Calcd for $C_{18}H_{16}O_6$ (328): C, 65.85; H, 4.91. Found: C, 65.66; H, 5.19.

Fractions 7-15 with R_f values of 0.46 were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.95 g (32% recovery) of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester as a clear oil: IR (1534) and ^1H NMR (5163) ($CDCl_3$) were identical to those of purified material from HPLC purification. (See later section)

After the samples had been collected, the column was flushed with 500 mL of ethyl acetate and 500 mL of diethyl ether. In this way, the column was reusable for as many as 7 times.

B. Kugelrohr distillation after acid and base washes.

Twenty grams (0.102 mol) of crude 2-(2-hydroxyethoxy)-benzoic acid, methyl ester was dissolved in 200 mL of methylene chloride. The organic solution was washed with 3 x 100 mL of 10% aqueous hydrochloric acid, 3 x 100 mL of 10% aqueous sodium bicarbonate, 2 x 100 mL of saturated aqueous sodium chloride, and 1 x 100 mL of water and then dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil, contained in a 250-mL round-bottomed flask, was transferred immediately to a kugelrohr apparatus and a vacuum applied. The brown oil was

distilled to afford 10.0 g (50% recovery) of a clear yellow oil: bp 110-140° / 0.1 mm Hg; IR (1703) and ^{1}H NMR (5613) ($CDCl_3$) identical to those of material obtained from HPLC and identified as 2-(2-hydroxyethoxy)-benzoic acid, methyl ester. (See later section)

C. Kugelrohr Distillation without the Acid and Base Washes

A solution of 20 g (0.102 mol) of crude 2-(2-hydroxyethoxy)-benzoic acid, methyl ester in 100 mL of methylene chloride was dried ($MgSO_4$) and then evaporated under reduced pressure until all foaming and bubbling stopped. The 250-mL round-bottomed flask was immediately transferred to a kugelrohr distillation apparatus and a vacuum was applied. The dark oil was distilled to afford 10.0 g (50% recovery) of a mixture of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester and monolactone: bp 110-120° / 0.1 mm Hg; ^{1}H NMR (5702) ($CDCl_3$) 8.0-6.8 (m, aromatic), 4.5 (s, OCH_2CH_2O), 4.3-3.6 (m, OCH_2CH_2OH), 3.8 (s, OCH_3); TLC, diethyl ether as the eluent, showed 2 components in the oil having R_f values of 0.60 and 0.40, corresponding to the monolactone and 2-(2-hydroxyethoxy)-benzoic acid, methyl ester, respectively.

D. Vacuum-line Distillation

A vacuum-line was adapted to accept a 250-mL round-bottomed flask with a Claisen head adapter. In the round-bottomed flask was placed 125 mL of crude ester. The system was evacuated and the ester heated to a gentle boil. A hot air gun was placed at the first joint on the manifold to keep the distillate from condensing at this point. The clear yellow ester was collected in a 250-mL round-bottomed flask, adapted for the manifold, in an ice/water bath. Two sets of U tubes were attached to the manifold immediately after the collection flask. The first U tube was immersed in a dry ice/acetone bath and the second was immersed in a liquid nitrogen bath. During the distillation procedure, these were routinely emptied of foul smelling, unidentified liquids. A typical recovery for this type of distillation was approximately 40%, and 300 mL of the partially purified ester was collected in 2 h. The yellow oil collected was shown to be a mixture of monolactone and 2-(2-hydroxyethoxy)-benzoic acid, methyl ester: bp 100-110° / 0.01-0.1 mm Hg; IR (4796) and ^{1}H NMR (9805) ($CDCl_3$) were identical to those of the material purified by kugelrohr distillation. Again the lactone peak is noted in the ^{1}H NMR at 4.5-4.6 as a singlet.

The residue from these distillations, 300 mL, was taken up in 400 mL of carbon tetrachloride. A white solid

material was collected by suction and recrystallized from ethanol/water to afford the dilactone: mp 164-165°; mmp 164-165°; IR (4798) and ^{1}H NMR (9806) ($CDCl_3$) were identical to those of dilactone purified by flash chromatography. Approximately 100 g of dilactone was obtained in this manner.

E. HPLC of Crude Sample

A solution of 20 g of crude 2-(2-hydroxyethoxy)-benzoic acid, methyl ester in 15 mL of ethyl acetate/15 mL hexane was injected onto the HPLC column. The flow rate was set at 250 mL/min, and samples were collected in 250-mL portions with a mixture of 40% ethyl acetate/60% hexane as the eluent. After a total of 10 samples had been collected (2.5 l), the system was flushed with 700 mL of ethyl acetate. TLC analysis, diethyl ether as the eluent, showed 2 components were separated from the crude oil with R_f values of 0.75 and 0.48, which correspond to the dilactone and 2-(2-hydroxyethoxy)-benzoic acid, methyl ester, respectively. Samples 3-5 with R_f values of 0.75 were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 1.3 g (6.5% recovery) of dilactone: mp 165-166°; mmp 164-166°; ^{1}H NMR (9807) ($CDCl_3$) identical to that of material obtained from flash chromatography.

Anal. Calcd for $C_{18}H_{16}O_6$ (328): C, 65.85; H, 4.91. Found: C, 65.85; H, 4.98.

Fractions 7-10 with R_f values of 0.47 were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 6.0 g (30%) of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester: IR (2785) 3600-3120 (alcohol OH), 3100 (aromatic C-H stretching), 3000-2850 (aliphatic C-H stretching), 1720 (ester C=O), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend), 760 (o-substitution); ^1H NMR (7392) ($CDCl_3$) 7.9-6.9 (m, 4, aromatic), 4.3-3.8 (m, 5, OCH_2CH_2OH), 3.8 (s, 3, OCH_3); ^{13}C NMR (4993) ($CDCl_3$) 166.73, 159.00, 133.83, 131.62, 121.02, 120.50, 115.23, 71.79, 60.93, 52.08; MS (395) 196 (32), 166 (41), 120 (100), 92 (67), 44 (7); UV (1280) (methanol) 204.5 (24,200), 229.5 (5160), 287.5 (2400).

Anal. Calcd for $C_{10}H_{12}O_4$ (196): C, 61.22; H, 6.15. Found: C, 61.13; H, 6.20.

F. HPLC of Vacuum-line Distilled Material

A solution of 20 g of vacuum-distilled 2-(2-hydroxyethoxy)-benzoic acid, methyl ester in 15 mL of ethyl acetate/15 mL hexane was injected onto the HPLC column. The flow rate was set at 250 mL/min, and samples were collected in 250-mL portions with a mixture of 40% ethyl acetate/60% hexane as the solvent. TLC analysis, diethyl ether as the eluent, showed 3 components separated from the original mixture. R_f values of 0.75, 0.66, and 0.48 correspond to the dilactone, monolactone, and 2-(2-hydroxyethoxy)-benzoic acid, methyl ester, respectively.

Fractions containing substances with identical R_f values were then combined. Fractions 2 and 3 (R_f = 0.75) were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 2.0 g (10%) of dilactone: mp 164-165°; mmp 164-165°; ^1H NMR (9808) ($CDCl_3$) was identical to that of the material obtained from flash chromatography.

Fractions 4 and 5 (R_f = 0.66) were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 2.0 g (10%) of monolactone: IR (3963) and ^1H NMR (8967) ($CDCl_3$) were identical to those of material prepared from 2-(2-hydroxyethoxy)-benzoic acid.

Fractions 6-11 (R_f = 0.48) were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 12.0 g (60%) of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester: IR (3963) and ^1H NMR (8969) ($CDCl_3$) were identical to those of material obtained from the previous HPLC purification of the crude material.

Base Hydrolysis of 2-(2-Hydroxyethyoxy)-benzoic Acid, Methyl Ester.

A mixture of 20 g (0.102 mol) of vacuum distilled 2-(2-hydroxyethoxy)-benzoic acid, methyl ester and 100 mL of 20% aqueous sodium hydroxide in a 250-mL round-bottomed flask, stirred at room temperature for 2 h, warmed as the solution became homogeneous. A solid, formed after the solution had become homogeneous, was removed by filtration

to afford 2.0 g of an unknown substance. The filtrate was diluted with 40 mL of water and extracted with 3 x 30 mL of methylene chloride. The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford no material. The aqueous phase was chilled in an ice bath and acidified with concentrated hydrochloric acid while the temperature was maintained between 0-5°. The acidified heterogeneous mixture was stirred for 1.5 h and warmed to room temperature. The mixture was extracted with 3 x 30 mL of methylene chloride, the organic extracts were combined, washed with 2 x 50 mL of water, dried ($MgSO_4$), and evaporated under reduced pressure to afford 12.9 g (70%) of 2-(2-hydroxyethoxy)-benzoic acid as a clear oil: IR (4767) and ^1H NMR (9775) ($CDCl_3$) were identical to those of material prepared from 2-(2-hydroxyethoxy)-benzamide.

Lactonization of 2-(2-Hydroxyethoxy)-benzoic Acid to Monolactone via the Brewster/Ciotti Method.[114]

A solution of 10.0 g (0.054 mol) of 2-(2-hydroxyethoxy)-benzoic acid dissolved in 100 mL of chilled pyridine was treated with 21.0 g (0.109 mol) of p-toluenesulfonyl chloride. The clear yellow solution was stirred between 0-5° for 2 h and then poured into 400 mL of water. This was extracted with 3 x 40 mL of chloroform, the organic layers were combined, dried

($MgSO_4$) and evaporated under reduced pressure. The resulting yellow liquid was treated with toluene and evaporated under reduced pressure until all the pyridine was removed. The remaining oil was dissolved in chloroform, dried ($MgSO_4$), and evaporated under reduced pressure to afford 8.1 g (75%) of monolactone: IR (1871) and ^1H NMR (5931) ($CDCl_3$) showed monolactone and impurities.

A portion was distilled in a kugelrohr apparatus to afford the purified monolactone as a clear yellow liquid: bp 110-125° / 0.1 mm Hg; IR (3282) 3090 (aromatic C-H stretching), 3000-2800 (aliphatic C-H stretching), 1720 (lactone C=O), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend), 760 (o-subsitution); ^1H NMR (6050) ($CDCl_3$) 7.9-6.9 (m, 4, aromatic), 4.5 (s, 4, OCH_2CH_2O); ^{13}C NMR (7043) ($CDCl_3$) 169.00, 154.78, 134.87, 133.37, 122.58, 121.02, 119.39, 70.88, 65.46; MS (524) 164 (77), 120 (22), 105 (100), 78 (10), 76 (36); UV (1281) (methanol) 204.5 (28,500), 233 (6700), 293 (2900).

Anal. Calcd for $C_9H_8O_3$ (164): C, 65.85; H, 4.91. Found: C, 65.66; H, 4.90.

Identical results were obtained following the procedure outlined above when 2.5 g of 2-(2-hydroxyethoxy)-benzoic acid was used; crude yield 91%. Kugelrohr distillation afforded 1.2 g (50%) of a white solid identified as the monolactone: mp 35-36°; IR (3282), ^1H NMR (9809) ($CDCl_3$), ^{13}C NMR (6936) ($CDCl_3$), and

MS (531) were all identical to the liquid monolactone. Recrystallization of the material was not successful.

Anal. Calcd for $C_9H_8O_3$ (164): C, 65.85; H, 4.91. Found: C, 66.24; H, 4.86.

Lactonization of 2-(2-Hydroxyethoxy)-benzoic Acid, Methyl Ester via Al_2O_3.

A 500-mL round-bottomed flask was charged with 50 g of neutral Al_2O_3, 75 mL of methylene chloride, and 0.50 g (0.00255 mol) of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester. The mixture was stirred at room temperature for 2 days, after which the Al_2O_3 was removed from the organic layer by filtration. The methylene chloride solution was dried ($MgSO_4$) and evaporated under reduced pressure to afford 0.40 g (96%) of 2,3-dihydro-5H-1,4-benzodioxepin-5-one (monolactone) as a clear oil: IR (4759) and ^1H NMR (9762) ($CDCl_3$) were identical to those of material prepared from 2-(2-hydroxyethoxy)-benzoic acid.

Preparation of 5-Bromo-2-(2-hydroxyethoxy)-benzoic Acid, Methyl Ester.

A solution of 3.0 g (0.015 mol) of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester, 10 mL of glacial acetic acid, and 3 mL (0.75 mol) of bromine was stirred at room temperature for 12 h. The red solution was poured into 50 mL of saturated aqueous sodium

metabisulfite, and the mixture was extracted with 3 x 30 mL of methylene chloride. The combined organic extracts were washed with 3 x 30 mL of 5% aqueous sodium bicarbonate and 2 x 30 mL of water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford 4.0 g (97%) of a yellow oil. This was distilled in a kugelrohr apparatus to afford 3.5 g (85%) of 5-bromo-2-(2-hydroxyethoxy)-benzoic acid, methyl ester: bp 110°/0.5 mm Hg; IR (5039) 3600-3200 (OH stretching), 3100 (aromatic C-H stretching), 3000-2880 (aliphatic C-H stretching), 1730 (ester C=O), 1600, 1570 (aromatic C=C stretching), 1300-1000 (C-O bend); ^1H NMR (10073) ($CDCl_3$) 7.8-6.8 (m, 3, aromatic), 4.4-3.3 (m, 8, OCH_2CH_2OH and OCH_3); ^{13}C NMR (7511) ($CDCl_3$) 165.17, 157.96, 136.37, 134.09, 121.93, 116.73, 112.95, 71.85, 60.73, 52.28; MS (560) 276, 274 (16), 200, 198 (100), 172, 170 (25), 120 (10), 63, (55); UV (1370) (methanol) 232 (8760), 303.5 (2200).

Anal. Calcd for $C_{10}H_{11}BrO_4$ (275): C, 43.63; H, 4.00. Found: C, 43.65; H, 3.80.

Preparation of 2-(2-Acetoxyethoxy)-5-bromobenzoic Acid, Methyl Ester.

A mixture of 10.0 g (0.051 mol) of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester, 25 mL of glacial acetic acid, and 7 mL of bromine was stirred for 16 h at room temperature. The clear red solution was

gently warmed to 50° for 0.5 h and then cooled to room temperature and extracted with 3 x 30 mL of diethyl ether. The organic layers were combined, washed with 10% aqueous sodium metabisulfite, once with 30 mL of water, dried ($MgSO_4$), and evaporated under reduced pressure to afford 11.0 g (68%) of crude 2-(2-acetoxyethoxy)-5-bromobenzoic acid as a yellow oil. This was purified by kugelrohr distillation: bp 115-125° / 0.1 mm Hg; IR (1995) 3090 (aromatic C-H stretching), 3000-2850 (aliphatic C-H stretching), 1740-1700 (ester C=O), 1600, 1580 (aromatic C=C stretching), 1300-1200 (acetate); ^1H NMR (6235) ($CDCl_3$) 8.0-6.8 (m, 4, aromatic), 4.6-4.1 (m, 4, OCH_2CH_2O), 3.8 and 2.0 (2s, 6, 2 CH_3); ^{13}C NMR (4885) ($CDCl_3$) 170.70, 165.17, 157.11, 136.43, 135.91, 134.09, 122.77, 116.01, 113.02, 67.63, 62.36, 52.15, 20.74; MS (537) 318, 316 (6), 213 (22), 200, 198 (33), 87 (100).

Anal. Calcd for $C_{12}H_{13}O_5Br$ (317): C, 45.42; H, 4.10. Found: C, 45.34; H, 4.14.

The oil solidified at room temperature after several weeks. Attempts at recrystallization of the solid from several solvent combinations met with failure. ^1H NMR (6275) ($CDCl_3$) of the solid was identical to the spectrum obtained from the liquid sample.

Preparation of 2-(2-Acetoxyethoxy)-5-bromobenzoic Acid.

A mixture of 1.4 g (0.0077 mol) of 2-(2-hydroxyethoxy)-benzoic acid, 0.75 mL (0.024 mol) of bromine, and 20 mL of glacial acetic acid was stirred at room temperature for 24 h. This was diluted with 100 mL of water and extracted with 3 x 30 mL of methylene chloride. The organic extracts were combined and washed with 30 mL of saturated aqueous sodium metabisulite, once with 30 mL of water, dried ($MgSO_4$), and evaporated under reduced pressure to afford a clear yellow liquid which solidified. The solid was recrystallized twice from ethyl acetate/cyclohexane to afford 2.0 g (85%) of 2-(2-acetoxyethoxy)-5-bromobenzoic acid: mp 90-92°; IR (4805) 3300-2500 (carboxylic acid OH), 3100 (aromatic C-H stretching), 2980-2900 (aliphatic C-H stretching), 1720, 1690 (ester and carboxylic acid C=O), 1600, 1570 (aromatic C=C stretching), 1300-1200 (acetate); ^1H NMR (8172) ($CDCl_3$) 10.3-10.1 (br s, 1, COOH), 8.4-6.9 (m, 3, aromatic), 4.5 (s, 4, OCH_2CH_2O), 2.1 (s, 3, CH_3); ^{13}C NMR (5728) ($CDCl_3$) 170.91, 165.25, 157.84, 137.16, 135.02, 123.31, 117.33, 113.75, 69.01, 62.83, 20.63; MS (535) 304, 302 (2), 87 (100), 63 (20).

Anal. Calcd for $C_{11}H_{11}BrO_5$ (303): C, 43.59; H, 3.65. Found: C, 44.10; H, 3.62.

Hydrolysis of 5-Bromo-2-(2-hydroxyethoxy)-benzoic Acid, Methyl Ester.

A solution of 0.50 g (0.0018 mol) of 5-bromo-2-(2-hydroxyethoxy)-benzoic acid, methyl ester and 15 mL of 20% aqueous sodium hydroxide was heated at reflux for 4 h. The aqueous solution was cooled and extracted with 3 x 30 mL of methylene chloride. The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford no additional material. The aqueous solution was treated with concentrated hydrochloric acid until the solution was acidic (pH = 4). The solution was cooled in an ice bath and a solid precipitated from solution. It was collected by suction, recrystallized once from ethanol/water, and air-dried to afford 0.45 g (95%) of 5-bromo-2-(2-hydroxyethoxy)-benzoic acid: mp 134-135°; mmp 134-135°; IR (5046) identical to that of material prepared from the hydrolysis of 5-bromo-2-(2-hydroxyethoxy)-benzamide.

Attempted Dehydration of 2-(2-Hydroxyethoxy)-5-bromo-benzoic Acid with $POCl_3$.

A 25-mL round-bottomed flask was charged with 0.20 g of 2-(2-hydroxyethoxy)-5-bromobenzoic acid and 10 mL of $POCl_3$. The clear solution was heated at reflux for 4.5 h and was monitored by TLC analysis, diethyl ether as the eluent. TLC analysis indicated starting material as the

sole component in the reaction mixture after 4.5 h. The solution was poured into 80 mL of crushed ice and water, and this mixture was then stirred until it became homogeneous. A solid which precipitated from the solution was collected by suction, recrystallized from water, and air-dried to afford 0.19 g of 2-(2-hydroxyethoxy)-5-bromobenzoic acid: mp 132-133°; mmp 132-133°.

Lactonization of 5-Bromo-2-(2-hydroxyethoxy)-benzoic Acid to 5-Bromolactone.

In a 50-mL round-bottomed flask was placed 0.75 g (0.0039 mol) of p-toluenesulfonyl chloride and 30 mL of freshly distilled pyridine. When 0.5 g (0.0019 mol) of purified 5-bromo-2-(2-hydroxyethoxy)-benzoic acid was added, the clear solution immediately turned yellow. The yellow solution became colorless after being stirred 20 min; stirring was maintained for 24 h at room temperature. It was concentrated under reduced pressure to a volume of 8 mL, which was poured into 20 mL of cold water, with immediate formation of a white solid. After 5 min, the solid was collected by suction, recrystallized from ethanol/water, and air-dried to afford 0.45 g (98%) of the 5-bromolactone: mp 99-100°; IR (3605) 3100 (aromatic C-H stretching), 2950 (aliphatic C-H stretching), 1700 (lactone C=O), 1600, 1480 (aromatic C=C stretching), 1300-1000 (C-O bend); ^{1}H NMR (8200) ($CDCl_3$) 8.1-6.8 (m, 3,

aromatic), 4.5 (s, 4, OCH_2CH_2O); ^{13}C NMR (6189) ($CDCl_3$) 167.58, 153.99, 137.06, 135.97, 122.97, 120.43, 114.90, 70.94, 65.68; MS (452) 244 (100), 242 (100), 200, 198 (31), 185, 183 (50), 156, 154 (12), 64 (81).

Anal. Calcd for $C_9H_7BrO_3$ (243): C, 44.47; H, 2.90. Found: C, 44.71; H, 2.93.

Attempted Bromination of Monolactone 30.

In a 25-mL round-bottomed flask was placed 0.5 g (0.003 mol) of purified lactone, 10 mL of glacial acetic acid and 0.5 mL (.009 mol) of bromine. The resulting clear red solution was stirred for 24 h at room temperature. It was extracted with methylene chloride (3 x 30 mL). The organic layer was washed with 50 mL of water, 50 mL of 5% aqueous $NaHSO_3$, and 50 mL of water and then dried ($MgSO_4$). The organic layer was concentrated under reduced pressure to afford 0.5 g of a clear liqud: IR (3241), ^1H NMR (8184), ^{13}C NMR (5746) were identical to those of the starting material.

Synthesis of 5-Bromolactone from Monolactone 30.

In a 50-mL round-bottomed flask was placed 15 mL of glacial acetic acid and 1 mL (0.019 mol) of bromine. To the dark red solution was added 0.5 g (0.003 mol) of purified lactone. The resulting red solution was stirred

for 18 h at room temperature. The reaction mixture was extracted with diethyl ether (3 x 30 mL). The ether solution was washed with 50 mL of water, 10% aqueous $NaHSO_3$ (2 x 20 mL), 50 mL saturated aqueous $NaHCO_3$, 50 mL water, and dried ($MgSO_4$). The organic layer was concentrated under reduced pressure to afford 0.5 g (70%) of the 5-bromolactone as a white solid: mp 74-78°; after recrystallization from ethanol/water, mp 99-100°; mmp 99-100°; IR (3244) and ^1H NMR (8194) ($CDCl_3$) were identical to those of material prepared from 5-bromo-2-(2-hydroxyethoxy)-benzoic acid.

Preparation of Dinitrolactone from 2-(2-Hydroxyethoxy)-benzoic Acid, Methyl Ester.

In a 150-mL beaker was placed 6.0 g (0.030 mol) of distilled 2-(2-hydroxyethoxy)-benzoic acid, methyl ester and a magnetic stirring bar. The ester was chilled to 5° in an ice bath. Cold, concentrated sulfuric acid (15 mL) was added to the chilled ester over a 5-min period. The reaction mixture became a dark brown, viscous oil after the addition of the acid, with the temperature of the mixture rising to 28°. It was then cooled to 5°.

A mixture of cold, concentrated nitric acid and sulfuric acid (10 mL/10 mL) was added to the dark oil by addition funnel over a period of 1.5 h, the temperature being maintained between 0-10°. Then the mixture was

stirred for 1 h at 0-10°. The resulting clear, orange-brown mixture was poured slowly into 600 g of crushed ice while vigorous stirring was maintained with a spatula. Solid formed immediately. The reaction mixture was refrigerated for 20 h. After the remaining ice had melted, the solid was collected by filtration, washed with 50 mL of distilled water and air-dried for 24 h to afford 6.0 g (77%) of crude off-white dinitrolactone. Recrystallization twice from acetone/diethyl ether gave the product in 51% yield: mp 169-170°; IR (2719) 3100 (aromatic C-H stretching), 2950-2850 (aliphatic C-H stretching), 1690 (lactone C=O), 1630, 1600 (aromatic C=C stretching), 1550, 1350 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (7197) (DMSO) 9.1-8.9 (dd, 2, aromatic), 5.0-4.7 (m, 4, OCH_2CH_2O); ^{13}C NMR (4821) (DMSO) 165.11, 151.71, 142.48, 140.01, 132.20, 124.01, 121.80, 73.55, 65.61; MS (518) 254 (100), 209 (40), 194 (74), 164 (8), 118 (34), 74 (35); UV (1189) (methanol) 215 (17,750), 272.5 (9600).

Anal. Calcd for $C_9H_6N_2O_7$ (254): C, 42.52; H, 2.36; N, 11.02. Found: C, 42.83; H, 2.14; N, 10.67.

In some instances an oily mass instead of an off-white solid was obtained after the oil had been added to the crushed ice. Careful addition and vigorous stirring seemed to prevent this from happening. If an oily mass was obtained, workup was still possible by decanting the aqueous layer and placing the residue into a flask so that recrystallization from acetone/diethyl ether could be

performed immediately. Yields were often much lower, but the product could be obtained in pure form.

It was very important to place the container with the ice/solid mixture into a refrigerator after addition and stirring were completed. In this way, the ice melted slowly while the organic material was kept cold. If the mixture was warmed to room temperature, oil formation resulted.

Attempted Mononitration of Monolactone.

A mixture of 1.0 g (0.0060 mol) of monolactone dissolved in 10 mL of glacial acetic acid, 0.5 mL of concentrated nitric acid, and 1 mL of concentrated sulfuric acid was stirred at room temperature for 17 h. The solution was poured into 100 g of crushed ice with the formation of an oil. The ice/water mixture was refrigerated until all the ice had melted. The liquid was extracted with 3 x 30 mL of methylene chloride; the organic extracts were combined, washed with 5% aqueous sodium bicarbonate until the aqueous phase was basic to litmus paper, once with 50 mL of water, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.9 g of the monolactone. TLC analysis, diethyl ether as the eluent, showed monolactone only, and spectral analysis indicated a recovery of the monolactone: IR (3510) identical to that of the starting material.

Preparation of Dinitrolactone by Nitration of the Monolactone.

Four grams (0.024 mol) of monolactone in a 150-mL beaker containing a magnetic stirring bar were cooled to 0-5° by means of an ice bath. Over a 5-min period, 10 mL of cold concentrated sulfuric acid were added dropwise. During the addition of the acid the temperature of the reaction mixture rose to 28° and the oil darkened in color. This was stirred and cooled again to 0-5°. A mixture of 10 mL of concentrated sulfuric acid and 10 mL of concentrated nitric acid was chilled and added to the reaction mixture over a period of 1 h, the temperature being maintained between 5-12°. Then the mixture was stirred for 1 h at 0-5°. The resulting clear orange mixture was poured slowly into 400 g of crushed ice while vigorous stirring was maintained with a spatula. Solid formed immediately. The reaction mixture was refrigerated for 2 days until the ice had melted. The solid was collected by suction, rinsed with 50 mL of water, 50 mL of diethyl ether, and recrystallized twice from acetone/diethyl ether to afford 5.1 g (83%) of the dinitrolactone: mp 169-170°; mmp 169-170°; IR (4396), ^{1}H NMR (9468) (DMSO), and ^{13}C NMR (6730) (DMSO) identical to those of material prepared from 2-(2-hydroxyethoxy)-benzoic acid, methyl ester.

Transesterification of Dinitrolactone to 3,5-Dinitro-2-(2-hydroxyethoxy)-benzoic Acid, Methyl Ester (HCl).

A 100-mL round-bottomed flask was charged with 3.0 g (0.0118 mol) of dinitrolactone, 50 mL of absolute methanol, and 3 drops of concentrated hydrochloric acid. The heterogeneous mixture was heated at reflux for 14 h, after 1 h the reaction mixture being a clear yellow solution. Cooled to room temperature, the solution was neutralized with aqueous saturated sodium bicarbonate (pH paper). At this point, the clear yellow solution changed to a bright canary yellow solution. The methanol was removed under reduced pressure until 5 mL of yellow liquid remained, to which was added 25 mL of water which resulted in an oily suspension that was stirred for 0.5 h at room temperature. The pH of the solution was tested and again enough aqueous saturated sodium bicarbonate was added until the pH of the solution was neutral when tested.

The aqueous solution was extracted with 3 x 20 mL of methylene chloride; the organic layers were combined, washed with 50 mL of water, dried ($MgSO_4$) and concentrated under reduced pressure to afford 3.2 g (95%) of the 3,5-dinitro-2-(2-hydroxyethoxy)-benzoic acid, methyl ester as a thick yellow oil: IR (3857) 3600-3200 (alcohol OH), 3090 (aromatic C-H stretching), 2990-2890 (aliphatic C-H stretching), 1730 (ester C=O), 1620, 1600 (aromatic C=C stretching), 1550, 1350 (nitro), 1300-1000 (C-O bend); ^1H

NMR (9023) ($CDCl_3$) 9.0-3.3 (dd, 2, aromatic), 4.4-3.8 (m, 4, OCH_2CH_2O), 3.6 (s, 3, $-OCH_3$), 3.3 (s, 1, OH); ^{13}C NMR (6714) (DMSO) 163.25, 155.90, 144.46, 141.40, 129.50, 126.90, 123.52, 60.04, 54.84, 53.35; MS (478) 254 (26), 226 (62), 210 (80), 194 (100), 152 (35), 118 (30), 74 (30); UV (1282) (methanol) 213.5 (21,250), 272.5 (12,000).

Anal. Calcd for $C_{10}H_{10}N_2O_8$: C, 41.97; H, 3.52; N, 9.79. Found: C, 41.72; H, 3.38; N, 9.67.

Attempted Transesterification of Dinitrolactone to 3,5-Dinitro-2-(2-hydroxyethoxy)-benzoic Acid, Methyl Ester(H_2SO_4).

To 3.0 g (0.01181 mol) of dinitrolactone and 50 mL of absolute methanol was added 5 drops of concentrated sulfuric acid. This mixture was heated at reflux for 3.5 h. After 1.5 h of heating, the reaction mixture was a clear yellow solution. Methanol was removed under reduced pressure until there remained in the reaction flask 5 mL of yellow liquid, which was taken up in 3 x 15 mL of methylene chloride. The combined extracts were washed with 50 mL of water and dried ($MgSO_4$). The methylene chloride was evaporated under reduced pressure to yield 3.0 g (100%) of a solid which was recrystallized from acetone/diethyl ether and identified as the dinitrolactone: mp 169-170°; mmp 169-171°, TLC analysis.

Preparation of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone and a solution of 0.10 g (0.10 mol) of sodium hydroxide in 25 mL of water was heated at reflux for 5 min, then chilled in an ice bath. The yellow heterogeneous mixture was filtered to afford 0.10 g (20%) of recovered dinitrolactone. The filtrate was treated with concentrated hydrochloric acid and left at room temperature. After 1 day, white crystals formed in the solution and were collected by suction to afford 0.30 g (70%) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid: mp 119-121°; IR (3607) 3600-2500 (carboxylic acid OH), 3540 (alcohol OH), 3100 (aromatic C-H stretching), 3100-2900 (aliphatic C-H stretching), 1740 (carboxylic acid C=O), 1610, 1590 (aromatic C=C stretching), 1550, 1360 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (9874) (DMSO) 8.9-8.6 (dd, 2, aromatic), 5.4-5.1 (br s, 2, COOH and OH), 4.4-3.6 (m, 4, OCH_2CH_2O); ^{13}C NMR (7039) (DMSO) 164.35, 156.03, 144.72, 141.68, 129.56, 128.07, 123.19, 78.90, 60.17; MS (453) 254 (100), 194 (67), 118 (30), 90 (18).

Anal. Calcd for $C_9H_8N_2O_8$ (272): C, 10.29; H, 39.72; N, 2.96. Found: C, 10.28; H, 39.91; N, 2.92.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone and 25 mL of 20% aqueous hydrochloric acid was refluxed for 3.5 h. The clear solution was cooled in an ice bath

and extracted with 3 x 30 mL of ethyl acetate. The organic extracts were combined and washed with 3 x 30 mL of water, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.50 g (93%) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid: mp 118-121°; mmp 117-120°; IR (4044) and ^1H NMR (9875) (DMSO) were identical to those of the material prepared by base hydrolysis.

Experimental results showed that the use of less than 20% aqueous hydrochloric acid resulted in the recovery of dinitrolactone. Neither method for the preparation of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid was always reproducible.

Preparation of 2-(2-Hydroxyethoxy)-benzamide.

A 250-ml flask was charged with 6.0 g (.030 mol) of distilled 2-(2-hydroxyethoxy)-benzoic acid, methyl ester (bp 120-150/0.1 mm Hg) and 100 ml of 30% ammonium hydroxide (1.65 mol) and stoppered. The heterogeneous mixture was stirred with a Teflon-coated magnetic stirring bar for 1 h until dissolution of the ester was noted. The mixture was first a milky color and then proceeded to turn clear yellow after complete dissolution of the ester. The reaction was followed by TLC, diethyl ether as the eluent, the ester having an R_f of 0.65 and the amide remaining near the baseline, R_f 0.10.

The resulting clear, yellow, aqueous solution was concentrated by evaporation until a yellow-brown, viscous oil remained. After the mixture had cooled to ambient temperature, crystallization was induced by scratching. The crude amide, 5.3-5.5 g (95-98%) yield, was recrystallized three times with diethyl ether/ethyl acetate (1:1, v/v) to yield the amide in 55-75% overall yield: mp 112-113° (lit[123] 114-116°); IR (2814) 3420-3200 (NH_2 and OH stretching), 3100 (aromatic C-H stretching), 2950 (aliphatic C-H stretching), 1665 (amide C=O), 1595 (aromatic bend), 1570 (NH bend), 1450 (C=C aromatic), 750 (o-substitution); ^1H NMR (7417) (acetone) 8.2-6.9 (m, 6, amide NH_2 and aromatics), 4.5-3.8 (m, 5, CH_2CH_2OH); ^{13}C NMR (3205) (acetone) 167.90, 158.34, 133.95, 132.46, 122.64, 121.73, 114.25, 71.66, 60.60; MS (213) 181 (10), 120 (100), 65 (10).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.35; H, 6.22; N, 7.45.

Other satisfactory methods of purification of the crude amide, although more tedious, were performed by sublimation and recrystallization from xylene.

Preparation of 2-(2-Hydroxyethoxy)-N-methylbenzamide from 2-(2-Hydroxyethoxy)-benzoic Acid, Methyl Ester.

A mixture of 4.0 g (0.020 mol) of purified 2-(2-hydroxyethoxy)-benzoic acid, methyl ester and 15 mL of 30%

aqueous methylamine was stirred in a 25-mL round-bottomed flask at room temperature for 24 h. The clear yellow solution was concentrated by means of a steam bath to afford a yellow oil. This was dissolved in 35 mL of acetone, dried ($MgSO_4$), and concentrated under reduced pressure to afford 3.9 g (98%) of 2-(2-hydroxyethoxy)-N-methylbenzamide as an oil which solidified upon cooling to room temperature. The solid was recrystallized twice from ethyl acetate/diethyl ether: mp 70-72°; IR (4276) 3600-3150 (alcohol OH and amide NH_2), 3100 (aromatic C-H stretching), 3000-2900 (aliphatic C-H stretching), 1640 (amide C=O), 1550 (N-H bend), 1300-1000 (C-O bend), 760 (o-substitution); ^1H NMR (9179) ($CDCl_3$) 8.3-6.9 (m, 4, aromatic), 4.3-3.8 (m, 6, OCH_2CH_2OH and N-H), 2.8, 2.9 (2 s, 3, NCH_3); ^{13}C NMR (6618) (acetone) 165.79, 165.66, 156.88, 132.62, 130.93, 122.86, 121.24, 114.22, 71.10, 59.52, 26.49, 26.36; MS (554) 195 (2), 165 (100), 134 (41), 121 (88), 65 (23).

Anal. Calcd for $C_{10}H_{13}NO_3$ (195): C, 61.53; H, 6.71; N, 7.17. Found: C, 61.60; H, 6.91; N, 7.07.

Preparation of N,N-Dimethyl-2-(2-hydroxyethoxy)-benzamide from 2-(2-Hydroxyethoxy-benzoic Acid, Methyl Ester.

A mixture of 4.0 g (0.020 mol) of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester purified by HPLC, and 25 mL of 25% aqueous dimethylamine was stirred at room temperature for 1 day. The clear yellow

homogeneous solution was poured into a large beaker and concentrated at steam bath temperature. The residual yellow oil was dissolved in 20 mL of acetone, dried ($MgSO_4$), and evaporated under reduced pressure to afford 4.1 g (99%) of N,N-dimethyl-2-(2-hydroxyethoxy)-benzamide as a thick yellow oil: IR (4275) 3600-3100 (alcohol OH), 3090 (aromatic C-H stretching), 3000-2800 (aliphatic C-H stretching), 1720 (ester C=O), 1620 (N-H bend), 1300-1000 (C-O bend), 760 (o-substitution); ^1H NMR (9180) ($CDCl_3$) 7.8-6.9 (m, 4, aromatic), 5.9-5.6 (br s, 2, OH and ?), 4.4-3.8 (m, 4, OCH_2CH_2O), 3.2, 3.0, 2.6 (3 s, 5, 2 CH_3); MS (534) 209 (22), 179 (47), 165 (30), 121 (100), 60 (88). The material was not examined further.

Aqueous Base Hydrolysis of 2-(2-Hydroxyethoxy)-benzamide.

A mixture of 3.0 g (0.0165 mol) of 2-(2-hydroxyethoxy)-benzamide and 100 mL of 20% aqueous sodium hydroxide was heated at reflux for 6 h. The clear solution was cooled to room temperature and extracted with 3 x 50 mL methylene chloride. The aqueous layer was acidified with concentrated hydrochloric acid and then extracted with 3 x 50 mL of methylene chloride. The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford 1.5 g (50%) of 2-(2-hydroxyethoxy)-benzoic acid as a clear oil: IR

(2000) identical to that of material prepared from aqueous acid hydrolysis of 2-(2-hydroxyethoxy)-benzamide.

Acid Hydrolysis of 2-(2-Hydroxyethoxy)-benzamide to 2-(2-Hydroxyethoxy)-benzoic Acid.

A 100-mL round-bottomed flask was charged with 4.5 g (0.025 mol) of 2-(2-hydroxyethoxy)-benzamide and 50 mL of 20% aqueous hydrochloric acid. The reaction mixture was heated at reflux for 24 h, cooled to room temperature, and extracted with 3 x 30 mL of methylene chloride. The organic extracts were combined and washed with 3 x 30 mL of saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 2 x 30 mL of methylene chloride and then carefully acidified with concentrated hydrochloric acid to pH 6 (pH paper).

The aqueous solution was extracted with 3 x 30 mL of chloroform; the organic layers were combined, dried ($MgSO_4$) and evaporated under reduced pressure to afford 3.0 g (67%) of 2-(2-hydroxyethoxy)-benzoic acid as a clear oil: IR (3072) 3600-2500 (alcohol OH and carboxylic acid OH), 3100 (aromatic C-H stretching), 3000-2890 (aliphatic C-H stretching), 1730 (carboxylic acid C=O), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend), 760 (o-substitution); ^1H NMR (7887) ($CDCl_3$) 8.2-6.9 (m, 6, aromatic, COOH, and OH), 4.4-3.9 (m, 4, OCH_2CH_2O); ^{13}C NMR (6983) ($CDCl_3$) 167.38, 158.15, 134.87, 132.98, 121.86,

118.46, 113.99, 71.33, 60.28; MS (523) 182 (4), 120 (100), 105 (73), 92 (83), 77 (36).

Anal. Calcd for $C_9H_{10}O_4$ (182): C, 59.34; H, 5.53. Found: C, 59.36; H, 5.48.

Preparation of 5-Bromo-2-(2-hydroxyethoxy)-benzamide from 2-(2-Hydroxyethoxy)-benzamide.

Three grams (0.075 mol) of sodium hydroxide was dissolved in 50 mL of water in a 100-mL round-bottomed flask and chilled to 0° in an ice bath. To the solution was added 3 mL (0.058 mol) of bromine which produced a clear red solution, which was stirred for 5 min at 0°. To the solution was added 6.0 g (0.033 mol) of purified 2-(2-hydroxyethoxy)-benzamide in portions over a 5-min period. The resulting mixture turned orange and then changed into a thick purple mass. This was stirred vigorously at 0° for 45 min and then for 1 h at room temperature. The purple mass was treated with 25 mL of saturated aqueous sodium metabisulfite. A white material was obtained from the reaction mixture after collection by suction. It was recrystallized once from water to afford 8.6 g (100%) of the 5-bromo-2-(2-hydroxyethoxy)-benzamide: mp 154-156° (lit[123] 159-160°); IR (1821) 3400-3000 (NH_2, OH), 3160 (aromatic C-H stretching), 2950 (aliphatic C-H stretching), 1680, 1610 (amide C=O and N-H bend), 1590 (aromatic C=C stretch), 1300-1000 (C-O bend); ^1H NMR

(9690) (acetone) 8.1-7.1 (m, 4.65, aromatic and NH_2), 4.4-3.8 (m, 3.95, OCH_2CH_2O), 2.8 (br s, 1.39, OH); ^1H NMR (9687) (DMSO) 8.1-7.1 (m, 4.97, aromatic and NH_2), 5.3-5.0 (m, 0.46, OH), 4.4-3.7 (m, 3.98, OCH_2CH_2O), 3.5 (s, 0.75, OH); ^{13}C NMR (5555) (acetone) 162.23, 158.41, 137.41, 135.15, 122.84, 117.90, 113.80, 72.31, 60.73; MS (517) 261, 259 (14), 231, 229 (43), 200, 198 (100), 172, 170 (30), 145, 143 (10), 63 (62).

Anal. Calcd for $C_9H_{10}BrNO_3$ (261): C, 41.56; H, 3.87; N, 5.38. Found: C, 41.70; H, 3.89; N, 5.31.

Preparation of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzamide.

A 100-mL round-bottomed flask was equipped with a thermometer and an addition funnel. To the flask containing 20 mL of concentrated sulfuric acid chilled to 0-5° was added 3.0 g (0.0165 mol) of 2-(2-hydroxyethoxy)-benzamide in small portions, the temperature of the reaction mixture being maintained between 0-5°. To the clear yellow solution was added a chilled mixture of 15 mL of concentrated nitric acid/15 mL concentrated sulfuric acid over a period of 0.5 h. The reaction temperature was maintained between 0-10° during the addition of the mixed acid. The clear solution was stirred at a temperature between 0-5° for 3 h and then poured into 400 g of crushed ice with vigorous stirring with a spatula. Addition of the solution to the ice resulted in the formation of a

white solid. The ice/solid mixture was refrigerated for 1 day until all the ice had melted. The solid was collected by suction and recrystallized once from ethanol to afford 4.3 g (95%) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzamide: mp 146-147°; IR (2740) 3500-3000 (NH_2 and OH stretching), 3100 (aromatic C-H stretching), 3000-2900 (aliphatic C-H stretching), 1680 (amide C=O), 1640-1590 (N-H bend and aromatic C=C stretching), 1350 (nitro), 1300-1000 (C-O bend); ^1H NMR (7259) (acetone) 8.6-7.2 (m, 4, aromatic and amide NH_2), 5.0-4.5 (m, 4, OCH_2CH_2O), 3.8-3.4 (br s, 1, OH); ^{13}C NMR (4896) (acetone) 164.65, 161.73, 142.74, 128.69, 128.30, 124.27, 114.58, 71.92, 67.30; MS (406) 254 (100), 210 (5), 194 (57), 106 (34), 74 (19).

Anal. Calcd for $C_9H_9N_3O_7$ (217): C, 39.86; H, 3.35; N, 15.49. Found: C, 39.68; H, 3.18; N, 15.09.

Preparation of 5-Bromo-2-(2-hydroxyethoxy)-benzoic acid from 5-Bromo-2-(2-hydroxyethoxy)-benzamide.

A 100-mL round-bottomed flask was charged with 2.0 g (0.0077 mol) of 5-bromo-2-(2-hydroxyethoxy)-benzamide and 50 mL of 20% aqueous hydrochloric acid. The mixture was heated to reflux, with complete dissolution of the solid. After the clear solution was refluxed for 6 h, the solution was filtered while hot. The white solid that formed in the cooled filtrate was collected by suction and recrystallized once from ethanol/water to afford 1.8 g

(90%) of 5-bromo-2-(2-hydroxyethoxy)-benzoic acid: mp 134-135°, IR (3059) 3600-3200 (alcohol OH), 3600-2500 (carboxylic acid OH), 3100 (aromatic C-H stretching), 3000-2900 (aliphatic C-H stretching), 1720 (carboxylic acid C=O), 1600, 1580 (aromatic C=C stretching), 1300-1200 (C-O bend); ^{1}H NMR (6266) (acetone) 8.2-7.1 (m, 3, aromatic), 6.1-5.9 (br s, 2, COOH and OH), 4.5-3.8 (m, 4, OCH_2CH_2O); ^{13}C NMR (5520) (acetone) 165.24, 158.41, 137.45, 135.13, 133.57, 122.84, 113.80, 72.89, 66.98; MS (422) 262, 260 (20), 198, 200 (100), 172, 170 (26), 63 (66).

Anal. Calcd for $C_9H_9BrO_4$ (261): C, 41.40; H, 3.47. Found: C, 41.32; H, 3.44.

Diazotization of 5-Bromo-2-(2-hydroxyethoxy)-benzamide.

A mixture of 0.50 g (0.0019 mol) of 5-bromo-2-(2-hydroxyethoxy)-benzamide and 5 mL of 25% aqueous hydrochloric acid was chilled in an ice bath. To this was added 2 mL of a dilute aqueous solution of sodium nitrite until a positive starch iodide test was obtained. The mixture was heated to boiling for 5 min, until gas evolution was complete. The green solution was placed in an ice bath, and a solid precipitated. It was collected by suction, recrystallized twice from ethanol/water, and air-dried to afford 0.40 g (80%) of 5-bromo-2-(2-hydroxyethoxy)-benzoic acid; mp 130-131°; mmp 130-132°; IR (5045)

identical to that of material prepared from the hydrolysis of 5-bromo-2-(2-hydroxyethoxy)-benzamide.

Conversion of 2-(2-Hydroxyethoxy)-benzamide to 2-(2-Hydroxyethoxy)-benzoic Acid by Diazotization.

A 1.0-g (0.0055 mol) sample of 2-(2-hydroxyethoxy)-benzamide was placed in 25 mL of 5% aqueous hydrochloric acid. The mixture was cooled in an ice bath and was treated with aqueous sodium nitrite until a positive starch iodide test was observed. The mixture was heated to boiling with the evolution of gas and total dissolution of the solid amide. The yellow solution was cooled and extracted with 3 x 30 mL of diethyl ether. The organic solutions were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford 0.70 g (70%) of a yellow oil identified as 2-(2-hydroxyethoxy)-benzoic acid: ^1H NMR (5893) ($CDCl_3$) was identical to that of the material prepared from 2-(2-hydroxyethoxy)-benzoic acid, methyl ester by saponification.

Preparation of Dinitrolactone by Diazotization of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzamide.

In a 150-mL beaker was placed 1.0 g (0.00369 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzamide and a 50-mL solution of 50% hydrochloric acid. The mixture was cooled in an ice bath to 0^o and then treated with an aqueous

solution of 1.0 g (0.0144 mol) sodium nitrite in 5 mL of water. The reaction mixture changed color to a brown-orange and gave a positive starch iodide test. It was heated at boiling for 15 min. Upon heating the mixture, brown gas was evolved and the solid material slowly dissolved producing a clear blue-green solution which then changed to clear yellow. The solution was chilled in an ice bath, then extracted with 2 x 30 mL of ethyl acetate. The organic layer was washed several times with water, then dried ($MgSO_4$), and concentrated under reduced pressure to yield an oil. The oil was treated with 2 mL of water and 5 mL of ethanol, the resulting mixture was chilled in an ice bath and scratched to induce crystallization. A white solid formed which was collected by suction and air-dried to yield 0.5 g of dinitrolactone: mp 167-168°; mmp 168-169°; IR (4149) was identical to that of material prepared from 2-(2-hydroxyethoxy)-benzoic acid, methyl ester.

From the filtrate was obtained an additional 0.4 g of dinitrolactone. Total yield 0.90 g (97%).

Acid Hydrolysis of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzamide to Dinitrolactone.

In a 100-mL round-bottomed flask was placed 2.0 g (0.007 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzamide and 50 mL of 10% aqueous hydrochloric acid. The

heterogeneous mixture was heated at reflux for 1.5 h during which time solid was present at all times. The mixture was filtered while hot and the solid air-dried to afford 1.8 g (quantitative) of the dinitrolactone: mp 167-172°; mmp 170-172°; IR (3841) identical to that of material prepared from the nitration of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester.

Attempted Dehydration of 2-(2-Hydroxyethoxy)-benzamide to 2-(2-Hydroxyethoxy)-benzonitrile with Acetic Anhydride.[126]

A. (3.5 h)

A 50-mL round-bottomed flask was charged with 1.0 g (0.0055 mol) of 2-(2-hydroxyethoxy)-benzamide and 20 mL of acetic anhydride. The mixture was heated at reflux for 3.5 h; then the acetic anhydride was removed under reduced pressure which afforded a clear oil: IR (2129) 2250 (nitrile), 1810, 1760 (anhydride C=O). Simple distillation of the material afforded 0.7 g of a clear oil: bp 174-175° / 1.4 mm Hg. A sample of the material was then distilled in a kugelrohr apparatus which afforded a mixture of products: bp 145° / 0.2 mm Hg; IR (2166) 3320 (N-H stretching), 3090 (aromatic C-H stretching), 3000-2880 (aliphatic C-H stretching), 2220 (nitrile), 1750, 1720, 1700 (carbonyls), 1300-1200 (acetate), 760 (o-substitution); ^{1}H NMR (6455) ($CDCl_3$) 7.8-6.9 (m, 4, aromatic), 4.7-4.2 (m, 4, OCH_2CH_2O), 2.2 (s, 3, CH_3). TLC

analysis, diethyl ether as the eluent, showed two components in the liquid with R_f values of 0.80 (faint) and 0.60.

B. (24 h)

A mixture of 2.0 g (0.0110 mol) of 2-(2-hydroxyethoxy)-benzamide and 20 mL of acetic anhydride was heated at reflux for 24 h. The acetic anhydride was removed by simple distillation and the remaining oil was placed under vacuum at room temperature for 8 h. The liquid was purified by kugelrohr distillation to afford 2.30 g of a clear liquid as a mixture of products: bp 140-165° / 0.4 mm Hg; IR (2325) 3320 (N-H stretching), 3080 (aromatic C-H stretching), 3000-2880 (aliphatic C-H stretching), 2220 (nitrile), 1750, 1720, 1700 (carbonyls), 1610, 1590 (aromatic C=C stretching), 1300-1200 (acetate), 760 (o-substitution); ^{1}H NMR (6676) ($CDCl_3$) 10.5-10.0 (br s, 1, N-H), 8.3-6.9 (m, 4, aromatic), 4.6-4.2 (m, 4, OCH_2CH_2O), 2.6, 2.1 (2 s, 6, 2 CH_3); MS (321) 265, 146, 132, 120, 76. No further experimentation was carried out.

Preparation of 5-Bromo-N-acetyl-2-(2-acetoxyethoxy)-benzamide.

A mixture of 1.0 g (0.0038 mol) of 5-bromo-2-(2-hydroxyethoxy)-benzamide and 15 mL of acetic anhydride was heated at reflux for 5 h. The clear solution was concentrated under reduced pressure to afford an oil which

crystallized at room temperature to yield 1.3 g of a waxy solid: mp 92-110°. A 0.70-g sample was recrystallized twice from ethanol to afford 0.65 g (93%) of purified 5-bromo-N-acetyl-2-(2-acetoxyethoxy)-benzamide: mp 118-120°; IR (4801) 3360 (N-H stretching), 3110 (aromatic C-H stretching), 1770, 1700 (ester and imide C=O), 1600 (aromatic C=C stretching), 1300-1000 (C-O bend), ^{1}H NMR (9815) (acetone) 10.5-9.9 (br s, 1, N-H), 8.2-7.2 (m, 3, aromatic), 4.6 (s, 4, OCH_2CH_2O), 2.5 and 2.1 (2 s, 6, 2 CH_3); ^{13}C NMR (6941) (acetone) 172.28, 171.04, 163.50, 156.80, 137.49, 134.89, 124.22, 116.55, 114.21, 68.55, 62.83, 25.96, 20.63; MS (536) 345, 343 (2), 185, 183 (3), 87 (100).

Anal. Calcd for $C_{13}H_{14}N_1O_5Br$ (344): C, 45.34; H, 4.07; N, 4.06. Found: C, 45.56; H, 4.20; N, 4.04.

Dehydration of 2-(2-Hydroxyethoxy)-benzamide to 2-(2-Hydroxyethoxy)-benzonitrile via Trifluoroacetic Anhydride/Pyridine.[128]

A solution of 20 mL of dioxane and 2.25 g (0.0124 mol) of 2-(2-hydroxyethoxy)-benzamide was chilled in an ice bath to 5°. To this was added 9.4 mL of dry pyridine and 4.0 mL of trifluoroacetic anhydride (TFAA). The temperature was maintained between 5-10° during the addition of the anhydride. The reaction mixture was stirred for 3 h at 0-5° and then extracted with 3 x 20 mL

of chloroform. The organic layers were combined, washed with 3 x 30 mL of water, once with 30 mL of brine, dried ($MgSO_4$), and evaporated under reduced pressure to afford 2.0 g of yellow oil: IR (2727) 3500-2500 (alcohol OH and carboxylic acid OH), 3100 (aromatic C-H stretching), 3000-2850 (aliphatic C-H stretching), 2240 (nitrile), 1740, 1690 (carbonyls), 1300-1200 (acetate and C-O bend).

The oil was dissolved in 25 mL of a solution containing 5 g sodium hydroxide/5 mL water/20 mL methanol and then stirred at room temperature. The methanol was evaporated under reduced pressure and then 50 mL of water was added. The aqueous solution was extracted with 3 x 30 mL of chloroform; the organic layers were combined, washed with water until the aqueous solution was neutral to litmus paper, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.30 g of a clear oil. TLC analysis, diethyl ether as the eluent, showed the oil was a mixture of two components with R_f values of 0.70 and 0.10. Spectral analysis showed a mixture of products: IR (2738) 3600-3100 (alcohol OH), 3100 (aromatic C-H stretching), 3000-2900 (aliphatic C-H stretching), 2240 (nitrile), 1660 (amide ?), 1300-1000 (C-O bend), 760 (o-substitution); ^1H NMR (7248) ($CDCl_3$) 8.2-6.5 (4, m, aromatic), 4.4-3.0 (m, 5, OCH_2CH_2OH). No further experimentation was undertaken.

Dehydration of 2-(2-Hydroxyethoxy)-benzamide to 2-(2-Hydroxyethoxy)-benzonitrile via Dichlorocarbene.[129]

A mixture of 5.0 g (0.0276 mol) of 2-(2-hydroxyethoxy)-benzamide and 200 mL of chloroform in a 500-mL round-bottomed flask was heated to 55° until the solid had dissolved. To the solution were added 0.50 g (0.0022 mol) of benzyltriethylammonium chloride and 44 mL of 50% aqueous sodium hydroxide. The dark mixture was cooled and stirred at room temperature for 15 h. It was washed with 3 x 50 mL of water until the aqueous solution was no longer basic towards litmus paper. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to afford 5.2 g of a dark oil. TLC analysis, diethyl ether as the eluent, showed the reaction mixture contained 3 components with R_f values of 0.75, 0.47, and 0.3, along with baseline tar. (The 2-(2-hydroxyethoxy)-benzamide has an R_f value of 0.2 when diethyl ether is used as an eluent.)

The oil was dissolved in 10 mL of chloroform and placed on a column of Baker Silica Gel 7, 8 mm x 4 mm, and eluted with 300 mL of diethyl ether. The clear yellow filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to afford 4.2 g of a yellow oil. TLC analysis was identical to the aforementioned TLC analysis but without the baseline tar. Spectral analysis of the mixture showed several functional groups to be present:

IR (2566) 3600-3000 (alcohol OH), 3100 (aromatic C-H stretching), 3000-2900 (aliphatic C-H stretching), 2250 (nitrile), 1730 (aldehyde C=O), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend), 800 (C-Cl); ^{1}H NMR (6867) ($CDCl_3$) 8.2 (s, O-CHO), 7.8-6.9 (m, aromatic), 4.6-3.8 (m, OCH_2CH_2O and OCH_2CH_2Cl), 2.8 (s, OH); MS (355) 191, 183, 181, and 163.

Purification of the Products

A mixture of 4.0 g of the yellow oil and 100 mL of a solution containing 10 g sodium hydroxide/20 g water/90 mL methanol was stirred for 15 h at room temperature. The solution was filtered; the filtrate was diluted with 50 mL of water, and the methanol was evaporated under reduced pressure. The aqueous solution was extracted with 3 x 30 mL of chloroform, the extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford 1.5 g of a yellow oil. The material was distilled in a kugelrohr apparatus to afford 1.1 g of an oil: bp 133-145^o / 1.1 mm Hg. TLC analysis showed 2 components in the oil with R_f values of 0.75 and 0.47: IR (2620) 3600-3200 (alcohol OH), 3100 (aromatic C-H stretching), 3000-2880 (aliphatic C-H stretching), 2250 (nitrile), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend), 800 (C-Cl); ^{1}H NMR (7043) ($CDCl_3$) 7.7-6.9 (m, aromatic), 4.5-3.8 (m, OCH_2CH_2Cl), 3.0-2.6 (br s, OH).

A 0.70-g sample of the distilled yellow oil was dissolved in 20 mL of diethyl ether. The solution was placed onto a flash chromatography column packed with Baker Silica gel 7 (1.5" x 6.0") and eluted with 400 mL of diethyl ether, 20-mL fractions being collected. (The first 40 mL were discarded as a forerun.) TLC analysis showed that a substance with an R_f value of 0.75 was in fractions 1-5 and a second substance with an R_f value of 0.47 was in fractions 9-17. Fractions 1-5 were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.3 g of 2-(2-chloroethoxy)-benzonitrile: mp 53-55°; IR (2635) 3100 (aromatic C-H stretching), 3000-2880 (aliphatic C-H stretching), 2250 (nitrile), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend); ^1H NMR (7059) ($CDCl_3$) 7.8-6.9 (m, 4, aromatic), 4.6-3.4 (m, 4, OCH_2CH_2Cl); ^{13}C NMR (4675) ($CDCl_3$) 159.78, 134.41, 133.96, 121.60, 116.01, 112.69, 102.55, 68.99, 41.16; MS (549) 183, 181 (17, 50), 119 (100), 91 (62), 63 (69).

Anal. Calcd for C_9H_8NOCl (182): C, 59.50; H, 4.43; N, 7.71. Found: C, 59.64; H, 4.45; N, 7.54.

Fractions 9-17 were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.4 g of 2-(2-hydroxyethoxy)-benzonitrile as a clear liquid: IR (2637) 3600-3100 (alcohol OH), 3100 (aromatic C-H stretching), 3000-2880 (aliphatic C-H stretching), 2250 (nitrile), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend); 760 (o-substitution); ^1H NMR (7061) ($CDCl_3$)

7.7-6.8 (m, 4, aromatic), 4.3-3.8 (m, 4, OCH_2CH_2O), 2.7 (s, 1, OH): ^{13}C NMR (4678) ($CDCl_3$) 175.58, 160.43, 134.41, 133.70, 121.21, 112.63, 102.16, 70.55, 60.93.

Treatment of the original mixture with NaI/acetone followed by aqueous base treatment

A 0.20-g sample of the reaction mixture which contained 3 components by TLC analysis was dissolved in 20 mL of a 15% sodium iodide/acetone solution. A finely divided solid began to precipitate from the reaction mixture within a few minutes. This mixture was heated to 50^{o} for 2 h with a noticeable increase of solid. The mixture was cooled, filtered through a cotton plug, and the acetone in the filtrate evaporated under reduced pressure. The residual solid/oil mixture was dissolved in a mixture of 5 g sodium hydroxide/10 g water/10 g methanol and stirred at room temperature for 15 h. To this was added 20 mL of water and the methanol removed under reduced pressure. This was extracted with 3 x 20 mL of chloroform, which was then washed with water until the aqueous solution was neutral to litmus paper, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.15 g of a yellow oil. TLC analysis of the oil indicated a mixture of 3 components with R_f values of 0.70, 0.47, and 0.10. Spectral analysis indicated a mixture of products: IR (2558) 3600-3100 (alcohol OH), 3100

(aromatic C-H stretching), 3000-2880 (aliphatic C-H stretching), 2240 (nitrile), 1650 (amide C=O), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend). The material was not investigated further.

Attempted Protection of the Alcohol in 2-(2-Hydroxy-ethoxy)-benzamide with Dihydropyran.

A solution of 0.5 g (0.0027 mol) of 2-(2-hydroxyethoxy)-benzamide, 1.0 g (0.011 mol) of dihydropyran, and 0.05 g (0.00027 mol) of p-toluenesulfonic acid in 20 mL of acetone was stirred at room temperature; the reaction was monitored by TLC analysis, with diethyl ether as the eluent. After 1 min the amide was the sole component in the reaction mixture with an R_f value of 0.10. After 15 min a new component was noted in the reaction mixture with an R_f value of 0.33. After 1 h another component was noted with an R_f value of 0.50. After the reaction mixture had been stirred for an additional hour, acetone was removed under reduced pressure to afford a yellow oil. This was dissolved in diethyl ether and washed with 3 x 30 mL saturated aqueous sodium chloride, 3 x 30 mL saturated sodium bicarbonate, and 3 x 30 mL of water, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.90 g of a yellow oil. Spectral evidence indicated a mixture of products: IR (2388) 3380 (N-H stretching), 3080 (aromatic

C-H stretching), 3000-2880 (aliphatic C-H stretching), 1710 (carbonyl), 1600 (aromatic C=C stretching), 1300-1000 (C-O bend), 760 (o-substitution); ^{1}H NMR (6774) ($CDCl_3$) 8.3-6.9 (m, aromatic), 5.1-3.3 (m, aliphatic), 2.1-1.3 (m, aliphatic). Similar results were obtained when only 1 equivalent of dihydropyran was used. TLC analysis indicated 3 components in the reaction mixture with R_f values of 0.10 (amide), 0.33, and 0.50. No further experimentation was pursued.

Purification of 2-(11-Hydroxy-3,6,9-trioxaundecyloxy)-benzoic Acid, Methyl Ester.

Kugelrohr Distillation

A crude 5.0-g sample of 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid, methyl ester was distilled in a kugelrohr apparatus. Vigorous foaming and frothing during distillation were minimized by first diluting the sample in 25 mL of methylene chloride and then removing the solvent at reduced pressure. Two fractions were collected: 120-155° / 0.1 mm Hg (0.5 g) and 150-200° / 0.1 mm Hg (2.0 g of a clear yellow oil). Spectral analysis, ^{1}H NMR (6052) ($CDCl_3$) and IR (4838), showed the first fraction to be a mixture of mostly aliphatic compounds. Spectral analysis of the second fraction showed it to contain mostly one component: IR (4839) 3600-3300 (alcohol OH), 3100 (aromatic C-H stretching),

3000-2800 (aliphatic C-H stretching), 1730 (ester C=O), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend); ^{1}H NMR (6070) ($CDCl_3$) 8.1-6.9 (m, 4, aromatics), 4.5-3.0 (m, 20, 4 OCH_2CH_2O, OCH_3, and OH).

A large scale purification performed by vacuum line manipulation, as described in the purification of 2-(2-hydroxyethoxy)-benzoic acid, methyl ester, was attempted. Because of the higher temperatures needed to distill the substance, the hot liquid had a tendency to bump and the greased joints often loosened. However, suitable material was obtained in this manner: ^{1}H NMR (6143) ($CDCl_3$) identical to that of the material obtained by kugelrohr distillation.

HPLC Purification

Twenty grams of vacuum-line distilled 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid, methyl ester was dissolved in 30 mL of acetone and placed on the HPLC column head. The flow rate was set at 250 mL/min, acetone as the solvent, and 10 samples were collected every 250 mL. TLC analysis, diethyl ether as the eluent, showed that fractions 2-4 had one component with an R_f value of 0.90 and the fifth fraction had a component with an R_f value of 0.20. Fractions 6-10 contained no components by TLC analysis. Fractions 2-4 were combined, dried ($MgSO_4$), and concentrated under reduced pressure, to afford 14.0 g of a yellow oil: ^{1}H NMR (9137) ($CDCl_3$) and IR (4837) were

identical to the material obtained from kugelrohr distillation.

Base Hydrolysis of 2-(11-Hydroxy-3,6,9-trioxaundecyloxy)-benzoic Acid, Methyl Ester.

Four grams (0.012 mol) of 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid, methyl ester was dissolved in 75 mL of an aqueous 5 M solution of sodium hydroxide. The yellow solution was heated at reflux for 4.5 h, chilled in an ice bath, and extracted with 3 x 30 mL of methylene chloride. The aqueous phase was chilled in an ice bath and acidified (pH = 6) with concentrated hydrochloric acid while the reaction temperature was maintained between 0-5°. The aqueous solution was extracted with 3 x 30 mL of methylene chloride, the organic extracts were combined, washed with 3 x 30 mL of water, dried ($MgSO_4$), and concentrated under reduced pressure to afford 3.2 g (84%) of 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid as a clear yellow oil: IR (4849) 3600-2500 (carboxylic acid OH and alcohol OH), 3100 (aromatic C-H stretching), 3000-2800 (aliphatic C-H stretching), 1730 (carboxylic acid C=O), 1610, 1590 (aromatic C=C stretching), 1300-1000 (C-O bend), 760 (o-subsitution); ^1H NMR (6097) ($CDCl_3$) 8.1-6.9 (m, 6, aromatic, COOH, and OH), 4.3-3.2 (m, 16, 4 OCH_2CH_2O). The material was not investigated further.

Preparation of 2-(11-Hydroxy-3,6,9-trioxaundecyloxy)-benzamide.

A mixture of 5.0 g (0.0152 mol) of 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid, methyl ester and 25 mL of 30% aqueous ammonium hydroxide was stirred at room temperature for 24 h. The aqueous solution was extracted with 3 x 30 mL of methylene chloride. The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford 3.4 g of a clear yellow oil identified as 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzamide: IR (3988) 3600-3100 (OH and NH_2), 3100 (aromatic C-H stretching), 3000-2800 (aliphatic C-H stretching), 1660 (amide C=O), 1600-1590 (aromatic C=C stretching), 1300-1000 (C-O bend), 760 (o-substitution); ^1H NMR (9015) ($CDCl_3$) 8.3-7.8 (m, 2, NH_2), 7.6-6.8 (m, 4, aromatic), 4.3-3.3 (m, 17.3, OCH_2CH_2O and 1 OCH_2CH_2OH). The material was not investigated further.

Attempted Lactonization of 2-(11-Hydroxy-3,6,9-trioxaundecyloxy)-benzoic Acid.

Two grams (0.0063 mol) of 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid was dissolved in 20 mL of pyridine and chilled in an ice bath to 0-5°. To the solution was added 2.5 g (0.013 mol) of p-toluenesulfonyl chloride in small portions over a 5-min period. The resulting solution was stirred at ice bath temperature for

1 h and then poured into 150 mL of ice/water. The aqueous solution was extracted with 3 x 30 mL of methylene chloride, the organic layers were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford a yellow oil. This was dissolved in 40 mL of toluene and concentrated under reduced pressure. The oil was then dissolved in 30 mL of methylene chloride, dried ($MgSO_4$), and evaporated under reduced pressure to afford 1.5 g (80%) of a yellow oil. Kugelrohr distillation of the material afforded 0.30 g of a clear yellow oil: IR (4857) and ^1H NMR (9871) ($CDCl_3$) appeared to be a mixture of materials. The pot residue was a black intractable tar. No further experimentation was pursued.

Attempted Nitration of 2-(11-Hydroxy-3,6,9-trioxaundecyloxy)-benzoic Acid, Methyl-Ester.

Six grams (0.018 mol) of distilled 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid, methyl ester was cooled to 0-5° by means of an ice bath. Over a 5-min period, 25 mL of cold concentrated sulfuric acid was added dropwise. During the addition of the acid the temperature of the reaction mixture rose to 25°. A chilled mixture of 10 mL of concentrated sulfuric acid and 10 mL of concentrated nitric acid was added to the reaction mixture over a period of 1 h, the temperature being maintained between 5-10°. The mixture was then stirred for 1 h at 0-

5°. The resulting clear orange solution was poured slowly onto 400 g of crushed ice, while vigorous stirring was maintained with a spatula. Solid formed immediately. The reaction mixture was refrigerated for 2 days until the ice had melted. The solid was collected by suction, rinsed with 50 mL of water, 50 mL of diethyl ether, and recrystallized twice from acetone/diethyl ether to afford 3.0 g of the same dinitrolactone prepared from 2-(2-hydroxyethoxy)-benzoic acid, methyl ester: mp 168-169°; mmp 168-170°; IR (1929) and ^{1}H NMR (6120) (DMSO) were identical to those of material prepared from 2-(2-hydroxyethoxy)-benzoic acid, methyl ester.

Degradation of 5-Bromo-2-(2-hydroxyethoxy)-benzoic Acid with BBr_3 to 5-Bromosalicyclic Acid.

In a dry, nitrogen-flushed 50-mL round-bottomed flask was placed 0.5 g (0.002 mol) of 5-bromo-2-(2-hydroxyethoxy)-benzoic acid and 10 mL of dry methylene chloride. The heterogeneous reaction mixture was stirred at room temperature for 10 min without complete dissolution of the acid. To the heterogeneous mixture was added 9 mL (0.009 mol) of 1 M BBr_3/methylene chloride (Aldrich) solution. After the addition, the reaction mixture had turned yellow and the solid had dissolved. The flask was flushed with nitrogen and the solution was stirred at room temperature. Progress of the reaction was

monitored by TLC by taking small aliquots of the reaction mixture, treating these with water, and extracting with methylene chloride. After 4 h, a faint blue spot, R_f (0.88), was noted by TLC (diethyl ether as eluent). Comparison of TLC behavior of the reaction mixture versus 5-bromosalicylic acid showed the two to be identical. The reaction mixture was stirred for an additional 44 h, then treated with 5 mL of water. This resulted in the formation of a solid in the flask. Stirring was continued for 1.5 h at room temperature. Then the contents of the flask were placed in a separatory funnel and extracted with 3 x 30 mL of diethyl ether. The organic layers were combined, washed with 3 x 50 mL of water, dried ($MgSO_4$), and evaporated under reduced pressure to yield 0.40 g of 5-bromosalicylic acid: mp 165-166°; mmp 165-167°; IR (3315) identical to that of material prepared from salicylic acid.

Preparation of 5-Bromosalicylic Acid.

Two grams (0.015 mol) of salicylic acid was placed in a 100-mL round-bottomed flask with 15 mL of glacial acetic acid and 1 mL (0.25 mol) of bromine. The resulting red solution was stirred at room temperature for 24 h. This was slowly added to 50 mL of a 10% aqueous solution of sodium metabisulfite from which formed a thick white slurry. The solid was collected by suction,

recrystallized once from water, and dried to yield 2.5 g (80%) of 5-bromosalicylic acid: mp 165-166° (lit.[346] 167-168°); IR (3314) identical to Sadtler spectrum (4568); ^{1}H NMR (9696) (acetone) identical to Sadtler spectrum (6758); ^{13}C NMR (5699) (acetone) 171.37, 162.80, 139.24, 133.19, 120.38, 114.86, 110.89.

Anal. Calcd for $C_7H_5BrO_3$ (217): C, 38.73; H, 2.32. Found: C, 38.33; H, 2.20.

Preparation of 2-Amino-3,5-dinitrobenzamide from Dinitrolactone.

A mixture of 0.5 g (0.00196 mol) of dinitrolactone and 50 mL of 30% aqueous ammonium hydroxide was heated and stirred at 70° until the white solid had completely dissolved and a yellow solid had precipitated from the solution. Heating was continued for an additional hour; the mixture was cooled in an ice bath, and the solid was collected by suction. It was recrystallized once from water to afford 0.40 g (90%) of 2-amino-3,5-dinitrobenzamide: mp 280-283° (lit[156] mp 284°), IR (2701) 3500-3200 (amine and amide NH_2 stretching), 3100 (aromatic C-H stretching), 1690 (amide C=O), 1640 (N-H bend), 1570, 1350 (nitro); ^{1}H NMR (7289) (DMSO) 9.5-9 (br s, 2, NH_2), 9.0-8.8 (dd, 2, aromatic), 8.7-8.4 and 8.2-7.8 (2 br s, 2, NH_2); ^{13}C NMR (5007) (DMSO) 168.45, 149.27, 133.33,

131.06, 129.95, 125.66, 118.31; MS (545) 226 (100), 209 (20), 117 (19), 90 (19), 62 (21).

Anal. Calcd for $C_7H_6N_4O_5$ (226): C, 37.28; H, 2.67; N, 24.77. Found: C, 37.46; H, 2.61; N, 24.42.

Treatment of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzamide with Aqueous Ammonium Hydroxide.

A 0.30-g sample (0.00106 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzamide was placed in 25 mL of aqueous 30% ammonium hydroxide. The mixture was stirred at room temperature for several hours with no apparent change. The heterogeneous mixture was heated at reflux for 1 h with the complete dissolution of the solid. The clear solution was then chilled in an ice bath. The precipitated solid was collected by suction to afford 0.30 g of the starting material: mp 146-147°; mmp 145-146°; IR (4784) identical to that of the starting material.

Attempted Ammonolysis of Dinitrolactone at Room Temperature.

A mixture of 0.5 g (0.00196 mol) of dinitrolactone and 20 mL of 30% aqueous ammonium hydroxide was stirred at room temperature for 0.5 h. The heterogeneous mixture was filtered and the solid was air-dried to afford 0.50 g of dinitrolactone: mp 165-166°; mmp 168-171°; ^1H NMR (7267) (acetone) identical to that of starting material.

Preparation of 3,5-Dinitrosalicylic Acid, Sodium Salt and Free Acid from Dinitrolactone.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone and a solution of 0.16 g (0.0040 mol) of sodium hydroxide in water was heated at reflux for 0.5 h, the result being a clear orange solution. This was cooled and treated with carbon dioxide or concentrated hydrochloric acid to afford 0.50 g (90%) of 3,5-dinitrosalicyclic acid, sodium salt which was then recrystallized from water: mp 320°; IR (3704) 3600, 3420 (phenolic OH), 3100 (aromatic C-H stretching), 1610, 1380 (carboxylic acid salt C=O), 1530, 1340 (nitro); ^{1}H NMR (8667) (DMSO) 8.7 (s, 2, aromatic), 3.9-3.5 (br s, 3, phenol OH and water).

Anal. Calcd for $C_7H_3N_2O_7Na \cdot H_2O$ (268): C, 31.36; H, 1.87; N, 11.44. Found: C, 31.31; H, 1.79; N, 11.44.

Experiments were performed where various ratios of base to dinitrolactone were used, different reaction temperatures, reaction times, and acid work ups. All gave as the product yellow salts, all being identical by IR analysis. Sadtler spectrum #46033 (purported to be the salt) has some similarity to the IR's obtained in this laboratory. It should be noted that the salt used for the Sadtler spectrum originated from Eastman Organic Chemicals, mp 172-174°. This corresponds to literature values for the melting point of the free carboxylic acid.

A mixture of 0.80 g (0.0029 mol) of 3,5-dinitrosalicyclic acid sodium salt from several experiments was combined and treated with 3 mL of concentrated sulfuric acid and 5 mL of water. A white solid formed from the yellow mixture. It was collected and recrystallized from water to afford 0.600 g (90%) of 3,5-dinitrosalicylic acid: mp 172-173° (lit[153] 172-174°); mmp 172-173°; IR (3691) identical to that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid, and Sadtler spectrum #17383; ^{1}H NMR (8772) (acetone) 9.1 (br s, 4, aromatic, phenol, and COOH) identical to Sadtler spectrum #12836.

Attempted Preparation of 3,5-Dinitrosalicylic Acid from 2-Chloro-3,5-dinitrosalicylic Acid.

A 1.0-g (0.0040 mol) sample of 2-chloro-3,5-dinitrobenzoic acid was placed in a 10 mL aqueous solution containing 0.40 g (0.01 mol) of sodium hydroxide. The mixture quickly darkened to a clear orange solution which was stirred at room temperature for 0.5 h. The solution was acidified with concentrated hydrochloric acid. The resulting solid was collected by suction and air-dried to yield 1.0 g of the starting material: mp 199-200°; mmp 198-200°.

Preparation of 3,5-Dinitrosalicylic Acid from 2-Chloro-3,5-dinitrobenzoic Acid.

A mixture of 1.0 g (0.0040 mol) of 2-chloro-3,5-dinitrobenzoic acid, 0.40 g (0.01 mol) sodium hydroxide, and 15 mL of water was heated at 60° for 0.5 h. The resulting clear yellow solution was cooled to room temperature at which point a yellow solid precipitated from the reaction mixture. This was dissolved by the addition of 10 mL of water. Acidification with concentrated sulfuric acid produced an off-white solid. The reaction mixture was cooled in an ice bath and the solid was collected by suction. It was recrystallized once from water and air-dried to afford 0.8 g (86%) of 3,5-dinitrosalicylic acid: mp 169-170° (lit[153] 171-172°); IR (4588) identical to Sadtler spectrum #17383.

Preparation of 3,5-Dinitrosalicylic Acid from 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester.

A 0.50-g (0.00174 mol) sample of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester was treated with 0.15 g (0.00375 mol) of sodium hydroxide dissolved in 15 mL of water. The clear red solution was heated to 80° for 0.5 h, cooled in an ice bath, and acidified with excess concentrated sulfuric acid. The precipitated solid was collected by suction and recrystallized once from water to afford 0.30 g (77%) of 3,5-dinitrosalicylic acid: mp 171-

172°; mmp 171-172°; IR (4802) identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Attempted Nucleophilic Displacement on Dinitrolactone with $Na_2S_2O_3$/Ethanol.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone and 0.50 g (0.0020 mol) of $Na_2S_2O_3 \cdot 5\ H_2O$ was dissolved in 15 mL of ethanol. The heterogeneous mixture was heated at reflux for 1 h, with the complete dissolution of all solid material. The clear yellow solution was chilled in an ice bath and a solid precipitated from solution. This was collected by suction and air-dried to afford 0.70 g of a waxy material: mp 132-135° sinters; IR (3882) 3600-3200 (alcohol OH), 3100 (aromatic C-H stretching), 3000-2920 (aliphatic C-H stretching), 1700 (carbonyl), 1550, 1350 (nitro), 1300-1000 (C-O bend); ^1H NMR (8951) (DMSO) 8.9-8.2 (m, aromatics), 4.4-4.0 (m, aliphatics), 3.6 (s, ?), 1.5-1.1 (m, aliphatic); ^{13}C NMR (6348) (acetone) 165.98, 160.95, 133.11, 131.42, 129.86, 124.85, 123.23, 119.13, 74.65, 72.83, 66.85, 66.39; MS (476) 209.

TLC analysis, diethyl ether as eluent, showed dinitrolactone as the sole reaction component.

Anal.: C, 46.66; H, 2.88; N, 8.45.

The pH of the reaction mixture was found to be slightly acidic. The reaction mixture also smelled of H_2S. Experiments were conducted where the reaction time

and percent of ethanol/water were varied. Dinitrolactone was recovered as the sole compound in each case. The material was not investigated any further.

Attempted Nucleophilic Displacement on the Dinitrolactone with $NaSH \cdot 9\ H_2O/NaHCO_3$.

A 100-mL round-bottomed flask was charged with 0.70 g (0.00275 mol) of dinitrolactone, 25 mL of 95% ethanol, 0.700 g of $NaSH \cdot 9\ H_2O$, and 0.20 g of $NaHCO_3$. The heterogeneous mixture was heated at 70° for 15 min. TLC analysis, diethyl ether as the eluent, showed one component in the reaction mixture after this time with an R_f value of 0.80. (R_f value of dinitrolactone 0.65.) The orange mixture was cooled to 5°, diluted with 5 mL of water, and then filtered. The filtrate was acidified with hydrochloric acid, and the resulting opaque yellow solution was extracted with 3 x 30 mL of methylene chloride. The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford 0.80 g of a yellow oil. TLC analysis showed one component with an R_f value of 0.80: IR (3563) 3600-3000 (alcohol OH), 3100 (aromatic C-H stretching), 3000-2900 (aliphatic C-H stretching), 1730 (carbonyl), 1550, 1350 (nitro), 1300-1000 (C-O bend).

The material was dissolved in 30 mL of diethyl ether and subjected to flash chromatography with diethyl ether

as the solvent. (Silica gel 7, Baker TLC reagent) Fractions were collected in 20-mL portions. TLC analysis showed fractions 4-8 contained several components which became intractable oils upon workup. Several attempts were made to characterize the substances. Preparative TLC was attempted to no avail. Each component when eluted on a preparative TLC plate produced several new components.

Experiments in which these reaction conditions and workups were altered all resulted in similar results, where the final products were intractable, dark oils. No further experimentation was pursued.

Attempted Nucleophilc Displacement on the Dinitrolactone with NaSH/EtOH.

A 100-mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was flame-dried. To the flask was added 25 mL of absolute ethanol and 0.20 g of sodium metal. Dry H_2S was bubbled through the clear sodium ethoxide solution for 0.5 h. To the clear yellow solution was added 0.50 g (0.00196 mol) of dinitrolactone. The mixture was stirred at room temperature for several minutes, with the reaction mixture turning a dark color. The ethanol solution was removed at reduced pressure to afford a dark oil. The oil was then treated in several ways.

Preparative TLC was attempted on 0.200 g of the dark oil, with diethyl ether as the eluent. This resulted in 12 bands of components as compared to one component by original TLC analysis. No further work was attempted in this manner.

A 0.20-g sample was dissolved in water and treated with aqueous hydrochloric acid until the solution was mildly acidic to pH paper. (pH = 6) This resulted in a dark, intractable oil.

No further experiments with NaSH were carried out. Experiments showed that, when the dinitrolactone was dissolved in hot ethanol and subjected to H_2S (gas), the dinitrolactone was recovered as the sole reaction component.

Attempted Nucleophilic Displacement on Dinitrolactone with $(NH_4)_2S$.

A 25-mL round-bottomed flask was charged with 0.30 g (0.0012 mol) of dinitrolactone and 5 mL of 20% aqueous (0.014 mol) $(NH_4)_2S$. After the resulting heterogeneous yellow mixture had been stirred at room temperature for 1 h, all solid had dissolved. Stirring was continued for an additional hour until a solid began to precipitate. It was collected by suction and rinsed with water to afford 0.10 g of an off white solid: mp 143-145°d; IR 3500-3000

(OH and NH_2), 3000-2800 (aliphatic C-H stretching), 1650 (amide C=O), 1350 (nitro), 1300-1000 (C-O bend).

Acidification of the filtrate caused precipitation of a solid, which was collectd by suction: mp 115-122° (polymeric sulfur ?); IR (3922) no absorptions.

When a solution of the dinitrolactone and aqueous $(NH_4)_2S$ was heated, there resulted a black solution that could not be characterized by any method. The results given above were not always reproducible and it should be noted that all filtrates turned black within minutes.

Preparation of Potassium Thiophenoxide in Methanol.

To a clear solution of 8 mL of absolute methanol and 2 mL (0.0194 mol) of benzenethiol was added 1.1 g (0.196 mol) of potassium hydroxide. The resulting mixture, which warmed spontaneously, was stirred vigorously until dissolution was complete.

Preparation of 2-Thiophenoxy-3,5-dinitrobenzoic acid from Dinitrolactone; Reflux Conditions.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone and 10 mL of absolute methanol was placed in a 25-mL round-bottomed flask. To this was added 0.9472 g (0.00640 mol) of potassium thiophenolate in 3.3 mL of absolute methanol. The reaction mixture was stirred at room temperature until the solid was completely dissolved. The

resulting clear, orange solution was heated to 50° for 15 min, cooled in an ice bath, and treated with 10% aqueous hydrochloric acid. The yellow solid which precipitated was collected by suction, rinsed with absolute methanol, and air-dried to afford 0.59 g (97%) of 2-thiophenoxy-3,5-dinitrobenzoic acid: mp 200-201°. This was recrystallized once from ethanol/water: mmp with an authentic sample 200-202°.

Preparation of 2-Thiophenoxy-3,5-dinitrobenzoic Acid from 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester and Isolation of the Spirocyclic Meisenheimer Complex.

A solution of 0.50 g (0.00174 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester in 5 mL of absolute methanol and a solution of 0.57 g (0.00388 mol) of potassium thiophenolate in 2 mL of absolute methanol were combined. After a 0.5-h stirring period at room temperature, a yellow solid had precipitated. A 0.5-mL aliquot was removed; the solid was collected by suction and rinsed several times with methanol to afford 0.05 g of the spirocyclic Meisenheimer complex: IR (4737) identical to that of material prepared from dinitrolactone.

The remaining solution was heated to reflux for 1 h, then cooled to room temperature and acidified with 5 mL of 10% aqueous hydrochloric acid. A solid formed which was collected by suction to afford 0.45 g (92%) of 2-

thiophenoxy-3,5-dinitrobenzoic acid: mp 199-200°; mmp 198-202°; IR (4731) identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 2-Thiophenoxy-3,5-dinitrobenzoic Acid from 2-Chloro-3,5-dinitrobenzoic Acid.

A mixture of 0.50 g (0.002 mol) of 2-chloro-3,5-dinitrobenzoic acid and 10 mL of absolute methanol was stirred at room temperature for 0.5 h and then treated with 0.65 g (0.0044 mol) of potassium thiophenolate in 2.2 mL of absolute methanol. The reaction mixture became bright yellow and turned into a thick paste which was stirred at room temperature for 1 h. To the reaction mixture was added 10 mL of water and 1 mL of hydrochloric acid which caused the color of the reaction to lighten to yellow. This slurry was stirred in an ice bath for 1 h, after which time the yellow solid was collected by suction and recrystallized once from ethanol/water to yield 0.63 g (97%) of 2-thiophenoxy-3,5-dinitrobenzoic acid: mp 200-202°; IR (4313) 3500-2500 (carboxylic acid OH), 3100 (aromatic C-H stretching), 1700 (carboxylic acid C=O), 1610, 1590 (aromatic C=C stretching), 1560-1530, 1350 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (8949) (acetone) 9.7-9.4 (br s, 1, COOH), 8.9-8.5 (dd, 2, aromatic), 7.3 (s, 5, aromatics); ^{13}C NMR (6338) (acetone) 165.04, 153.27, 146.84, 140.14, 139.03, 133.89, 132.72, 130.25,

129.47, 128.11, 122.58; MS (499) 320 (100), 210 (36), 182 (43), 166 (45), 125 (58), 77 (53).

Anal. Calcd for $C_{13}H_8N_2O_6S$ (320): C, 48.75; H, 2.51; N, 8.74. Found: C, 48.96; H, 2.57; N, 8.56.

Preparation of 2-Amino-3,5-dinitrobenzamide from 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester.

A 15-mL round-bottomed flask was charged with 0.50 g (0.00174 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester and 10 mL of 30% aqueous ammonium hydroxide. The reaction mixture first turned clear orange and then deposited a yellow solid after 5 min of stirring at room temperature. The solid was collected by suction, rinsed with water, and air-dried to afford, in quantitative yield, 0.39 g of 2-amino-3,5-dinitrobenzamide: mp 260-265°. This was recrystallized from water to afford the purified product: mp 282-284°; mmp 280-284°; IR (4205) and ^1H NMR (9183) (DMSO) were identical to those of the material prepared from dinitrolactone.

Preparation of 2-Methylamino-3,5-dinitro-N-methylbenzamide from Dinitrolactone.

To a stirred solution of 25 mL (0.3225 mol) of 40% aqueous methylamine was added 1.0 g (0.003937 mol) of dinitrolactone. The reaction mixture quickly darkened to

a deep red color. This heterogeneous mixture was stirred at room temperature for 68 h after which time 0.40 g of a yellow solid, A, was collected by suction and rinsed with water. The filtrate was allowed to evaporate at room temperature for 2 days. A solid formed in the filtrate, which was collected by suction and rinsed with water to afford an additional 0.60 g of yellow solid, B.

Solid A was recrystallized once from water and identified as 2-methylamino-3,5-dinitro-N-methylbenzamide: mp 174-175°; IR (3610) 3360-3300 (amide and amine N-H stretch), 3100 (aromatic C-H stretching), 3000-2900 (aliphatic C-H stretching), 1645 (amide C=O), 1620-1590 (amide N-H bend and aromatic C=C stretching), 1550, 1320 (nitro); ^{1}H NMR (8766) (acetone) 9.6-9.0 (br s, .5, N-H), 8.9-8.3 (dd, 2, aromatic), 8.3-7.8 (br s, .5, N-H), 3.2-2.8 (m, 7, 2 N-CH_3, and N-H); ^{13}C NMR (6276) (acetone) 167.84, 149.18, 134.80, 134.15, 129.60, 125.37, 124.53, 32.58, 26.85, 26.72; MS (451) 254 (44), 237 (100), 206 (59), 150 (42), 131 (46), 76 (70).

Anal. Calcd for $C_9H_{10}N_4O_5$ (254): C, 42.53; H, 3.97; N, 22.04. Found: C, 42.43; H, 3.99; N, 22.29.

Solid B, also recrystallized once from water, was identified as 2-methylamino-3,5-dinitro-N-methylbenzamide: mp 174-175°; mmp 174-175°. Total yield for the reaction was 1.0 g (99%).

Preparation of 2-Methylamino-3,5-dinitro-N-methylbenzamide from 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester.

In a 25-mL round-bottomed flask were placed 0.50 g (0.00174 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester and 10 mL of 30% aqueous methylamine. The clear red solution was stirred at room temperature and within 1 min a solid began to precipitate. The reaction mixture was stirred at room temperature for 8 h, after which time the orange solid was collected by suction, rinsed with water, and air-dried to afford 0.44 g (100%) of 2-methylamino-3,5-dinitro-N-methylbenzamide. The solid was recrystallized once from ethanol/water: mp 173-175°; mmp 173-175°; IR (4207) and ^{1}H NMR (9181) (acetone) were identical to those of the material prepared from dinitrolactone.

Preparation of 2-Dimethylamino-3,5-dinitro-N,N-dimethylbenzamide from 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester.

A mixture of 0.50 g (0.00174 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester and 10 mL of 25% aqueous dimethylamine was placed in a 25-mL round-bottomed flask and stirred at room temperature for 8 h. A solid, which precipitated from the clear red solution, was collected by suction, washed with 2 x 15 mL

of water, and air-dried to afford 0.40 g (82%) of a yellow solid. This was recrystallized once from ethanol/water to afford 2-dimethylamino-3,5-dinitro-N,N-dimethylbenzamide: mp 105-106°; mmp 106-107°; IR (4206) and ^{1}H NMR (9182) (acetone) were identical to those of the material prepared from dinitrolactone.

Preparation of 2-Dimethylamino-3,5-dinitro-N,N-dimethylbenzamide from Dinitrolactone.

To a stirred solution of 25 mL (0.138 mol) of 25% aqueous dimethylamine was added 1.0 g (0.003937 mol) of dinitrolactone, whereupon a deep red color was produced. The heterogeneous mixture was stirred at room temperature for 0.5 h without complete dissolution of the solid dinitrolactone. Heat was applied to the reaction mixture until the solid was dissolved. Trial extractions of the cooled aqueous solution with methylene chloride and diethyl ether afforded no material. The aqueous solution was allowed to evaporate at room temperature for 2 days during which time a yellow-orange solid formed in the reaction mixture. The material was recrystallized once from water and air-dried to yield 1.0 g (94%) of 2-dimethylamino-3,5-dinitro-N,N-dimethylbenzamide: mp 107-109°; IR (3608) 3080 (aromatic C-H stretching), 2950-2850 (aliphatic C-H stretching), 1650 (amide C=O), 1610, 1590 (aromatic C=C stretching), 1540, 1335 (nitro); ^{1}H NMR

(8579) (acetone) 8.7-8.1 (dd, 2, aromatic), 3.2 (s, 3, N-CH_3), 3.0-2.95 (2s, 9, N-CH_3 and $N(CH_3)_2$); ^{13}C NMR (6248) (acetone) 167.78, 147.94, 141.11, 138.51, 132.33, 128.04, 123.94, 42.59, 38.56, 34.92; MS (454) 282 (4), 190 (100), 146 (17), 102 (4).

Anal. Calcd for $C_{11}H_{14}N_4O_5$ (282): C, 46.81; H, 5.00; N, 19.85. Found: C, 46.87; H, 5.00; N, 19.68.

Attempted Nucleophilic Displacement on Dinitrolactone with Aniline at Room Temperature: (Neat).

A 10-mL round-bottomed flask was charged with 0.50 g (0.00196 mol) of dinitrolactone and 3 mL of freshly distilled aniline. The reaction mixture became homogeneous at room temperature after a short while. The clear orange solution was stirred at room temperature for 19 h, after which time a solid was present in the reaction mixture. It was treated with 5 mL of diethyl ether and stirred at room temperature for 15 min. The solid was collected by suction, rinsed with diethyl ether, and air-dried to afford 0.60 g of a yellow solid: mp 120-150°; IR (4041) 3500, 3400 (NH stretching), 3100 (aromatic C-H stretching), 3090-3000 (aliphatic C-H stretching), 1760, 1740, 1720 (carbonyls), 1550, 1350 (nitro), 1300-1000 (C-O bend). The substance was recrystallized from ethanol and found to be dinitrolactone: mp 168-170°; mmp 169-170°.

Attempted Nucleophilic Displacement on Dinitrolactone with Aniline at 45° and 100°: (Neat).

In a 15-mL round-bottomed flask was placed 0.50 g (0.00196 mol) of dinitrolactone and 3 mL of freshly distilled aniline. The orange mixture was heated to 45° at which point all solid was dissolved. The clear orange solution was heated at 45° for 3 h, then chilled in an ice bath and treated with 15 mL of diethyl ether. After 5 min of stirring the ether/aniline solution, a yellow solid precipitated from solution. It was collected by suction and rinsed several times with diethyl ether to afford 0.50 g of dinitrolactone: IR (4069) identical to the starting material.

A similar experiment was conducted at a reaction temperature of 100°. This resulted in an intractable black tar. No further work was pursued on this material.

Preparation of 2-Anilino-3,5-dinitrobenzoic Acid, Anilinium Salt from Dinitrolactone: (Ethanol/Aniline).

A mixture of 0.5 g (0.00196 mol) of dinitrolactone and 25 mL of 95% ethanol was heated to reflux. To the heterogeneous reaction mixture was added 0.2 mL (0.002 mol) of aniline, and heating was continued at reflux for 24 h. The resulting clear yellow solution was cooled to room temperature whereupon a solid precipitated. It was collected by suction and rinsed with ethanol to afford

0.20 g of dinitrolactone: mp 171-172°; mmp 170-171°; IR (4049) identical to that of the starting material.

The filtrate was concentrated under reduced pressure to afford an orange liquid which was dissolved in 3 mL of diethyl ether and chloroform. After the orange solution had been chilled in an ice bath, a yellow orange solid precipitated from the mixture to afford 0.30 g (65%) of 2-anilino-3,5-dinitrobenzoic acid, anilinium salt: mp 184-185°; IR (4051) was identical to that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Acidification of the Anilinium salt from Dinitrolactone to afford 2-Anilino-3,5-dinitrobenzoic Acid.

A 0.25-g (0.0063 mol) sample of 2-anilino-3,5-dinitrobenzoic acid, anilinium salt was placed in a 10-mL round-bottomed flask with 5 mL of 10% aqueous hydrochloric acid. The heterogeneous mixture was heated to 90° and stirred for 0.5 h, during which time the reaction color changed from orange to yellow. At no time did the solid dissolve completely. The yellow mixture was cooled in an ice bath; solid was collected by suction and air-dried to afford 0.15 g (80%) of 2-anilino-3,5-dinitrobenzoic acid: mp 213-214°; mmp 212-214°; IR (4073), ^{1}H NMR (9067) (acetone); ^{13}C NMR (6469) (acetone) and MS (502) were all identical to those of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 2-Anilino-3,5-dinitrobenzoic Acid, Anilinium Salt from 2-Chloro-3,5-dinitrobenzoic Acid.

A mixture of 2.0 g (0.0081 mol) of 2-chloro-3,5-dinitrobenzoic acid and 3 mL of freshly distilled aniline was placed in a 25-mL round-bottomed flask and flushed with nitrogen. The heterogeneous mixture was stirred at room temperature for 0.5 h, after which time 15 mL of diethyl ether was added. The orange solid was collected by suction, rinsed several times with diethyl ether, and recrystallized from ethanol to afford 2.3 g (72%) of 2-anilino-3,5-dinitrobenzoic acid, anilinium salt: mp 183-185°; IR (4008) 3100 (aromatic C-H stretching), 3300-2600 (anilium salt), 1600 (carboxylic acid salt C=O), 1500 (N-H bend), 1540, 1360 (nitro); ^{1}H NMR (9016) (acetone) 9.2-8.8 (dd, 3, nitroaromatics and N-H), 7.5-6.9 (m, 13, aromatics and NH_3^+); ^{13}C NMR (6412) (DMSO) 167.71, 144.33, 142.18, 139.59, 136.59, 135.81, 130.86, 129.56, 129.37, 126.18, 125.53, 121.43, 120.78, 120.00, 117.66.

Anal. Calcd for $C_{19}H_{16}N_4O_6$ (396): C, 57.57; H, 4.04; N, 14.14. Found: C, 57.46; H, 4.03; N, 14.16.

Acidification of the Anilinium salt to 2-Anilino-3,5-dinitrobenzoic Acid.

One gram (0.00252 mol) of the purified anilinium salt was placed in a 100-mL round-bottomed flask with 50 mL of 10% aqueous hydrochloric acid. The orange suspension was

stirred and heated to 45°, where the solid changed to a yellow color. The reaction mixture was heated at 45° for an additional 15 min and then cooled in an ice bath. The yellow solid was collected by suction, recrystallized from ethanol, and air-dried to afford 0.75 g (98%) of 2-anilino-3,5-dinitrobenzoic acid: mp 213-214°; IR (4072) 3260 (N-H stretching), 3200-2500 (carboxylic acid OH), 3100 (aromatic C-H stretching), 1690 (carboxylic acid C=O), 1600 (aromatic C=C stretching), 1550, 1350 (nitro); ^{1}H NMR (9668) (acetone) 10.9 (br s, 1, N-H), 9.9 (br s, 1, COOH), 9.1-8.8 (dd, 2, nitroaromatics), 7.3-6.9 (m, 5, aniline aromatics); ^{13}C NMR (6469) (acetone) 168.10, 145.40, 140.07, 138.19, 137.02, 131.94, 130.19, 127.91, 126.74, 121.28, 118.03; MS (502) 303 (100), 268 (19), 193 (16), 165 (40), 77 (26).

Anal. Calcd for $C_{13}H_9N_3O_6$ (303): C, 51.49; H, 2.99; N, 13.86. Found: C, 51.38; H, 2.93; N, 13.83.

Preparation of 1,3-Dinitroacridone.

A mixture of 2.0 g (0.0066 mol) of 2-anilino-3,5-dinitrobenzoic acid and 150 g of polyphosphoric acid was heated with stirring at 120° for 0.5 h. The dark, viscous mixture was cooled to 100° and then poured into 400 g of crushed ice, with the immediate formation of a yellow solid. After the ice had melted, the acidic mixture was treated with potassium carbonate until the solution was

neutral. The solid was collected by suction, rinsed several times with water, and air-dried to afford 1.5 g (80%) of a yellow solid. The solid was recrystallized from acetonitrile to afford 1.2 g (64%) of 1,3-dinitroacridone: mp 315-320° decomposed (lit[314] >350°); IR (5003) 3280 (NH stretching), 3100 (aromatic C-H stretching), 1645 (ketone carbonyl), 1620, 1610 (aromatic C=C stretching), 1530, 1340 (nitro); Due to the insolubility of the material ^{1}H NMR and ^{13}C NMR were not feasible.

Anal. Calcd for $C_{13}H_7H_3O_5$ (285): C, 54.75; H, 2.47; N, 14.73. Found: C, 54.17; H, 2.39; N, 14.51.

Preparation of 2-Methoxy-3,5-dinitrobenzoic Acid from Dinitrolactone.

A mixture of 1.0 g (0.0040 mol) of dinitrolactone and 15 mL of a solution of freshly prepared sodium methoxide (0.20 g sodium metal) was heated at reflux for 3 h with the formation of a yellow solid during this time. The mixture was cooled to room temperature and the solid removed by suction. The filtrate was concentrated under reduced pressure to afford a semisolid which was then diluted with 10 mL of water. The red solution was acidified with 3 N aqueous hydrochloric acid which caused a white solid to precipitate. It was collected, recrystallized twice from methanol/water and dried to

afford 0.70 g of 2-methoxy-3,5-dinitrobenzoic acid: mp 164-165°; mmp 164-165°; IR (3656); ^{1}H NMR (8789), ^{13}C NMR (6247) and MS (450) were identical to those of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 2-Methoxy-3,5-dinitrobenzoic Acid from 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic acid, Methyl Ester.

A 25-mL round-bottomed flask, equipped with a reflux condenser and magnetic stirring bar, was flame-dried and flushed with nitrogen. To the dry flask was added 15 mL of absolute methanol and 0.2 g of sodium metal. To the cooled clear solution of sodium methoxide was added 0.50 g (0.00174 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester dissolved in 2 mL of absolute methanol. The reaction mixture darkened, and an orange solid precipitated from the solution. The solid material from a 1-mL aliquot was collected by suction and rinsed several times with methanol to afford 0.075 g of 2-methoxy-2-(2-hydroxyethoxy)-Meisenheimer complex: IR (4738) identical to that of material prepared from dinitrolactone.

The remaining mixture was heated at reflux for 3 h, during which time the solution first became clear and then a yellow solid formed after 1.5 h. The solid was removed by suction filtration to afford 0.025 g (5%) of 2-methoxy-3,5-dinitrobenzoic acid, sodium salt: IR (5002) identical

to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

The filtrate was evaporated under reduced pressure to afford a maroon solid: IR (4740) identical to material prepared from 3,5-dinitrolactone. The solid was dissolved in 10 mL of water and treated with 5 mL of 10% aqueous hydrochloric acid. The precipitated solid was collected by suction and recrystallized from water to afford 0.35 g (85%) of 2-methoxy-3,5-dinitrobenzoic acid: mp 163-164°; mmp 162-164°; IR (4745) identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 2-Methoxy-3,5-dinitrobenzoic Acid from 2-Chloro-3,5-dinitrobenzoic Acid.

A solution of 1.1 g (0.0275 mol) sodium hydroxide in 15 mL of absolute methanol was added to 3.0 g (0.012 mol) of 2-chloro-3,5-dinitrobenzoic acid. The resulting clear liquid quickly changed to a clear red solution and within a few minutes a solid began to precipitate. The red mixture was stirred at room temperature for 1 h and then chilled in an ice bath. The yellow solid was collected by suction and rinsed several times with cold methanol to afford 0.2 g of a solid.

To the filtrate was added 1 mL of concentrated hydrochloric acid, causing a finely divided white solid to precipitate from the cold solution, presumably being

sodium chloride. The solid was removed by filtration, and to the filtrate was added water until a white solid was formed in the reaction flask. This was collected by suction and recrystallized from methanol/water to yield 2.0 g (68%) of 2-methoxy-3,5-dinitrobenzoic acid: mp 164-165° (lit[152] 165°); IR (4700) 3200-2500 (carboxylic acid OH), 3100 (aromatic C-H stretching), 2950 (aliphatic C-H stretching), 1700 (carboxylic acid C=O), 1620, 1590 (aromatic C=C stretching), 1560-1540, 1350 (nitro), 1300-1200 (C-O bend); ^{1}H NMR (9679) (acetone) 10.7 (s, 1, COOH), 3.8 (s, 2, aromatic), 4.15 (s, 3, OCH_3); ^{13}C NMR (6863) (acetone) 164.07, 158.22, 145.99, 142.93, 130.77, 128.82, 124.14, 65.16; MS (544) 242 (5), 194 (100), 120 (15), 92 (19), 74 (12).

Anal. Calcd for $C_8H_6N_2O_7$ (242): C, 39.68; H, 2.50; N, 11.57. Found: C, 39.42; H, 2.44; N, 11.40.

Attempted Nucleophilic Displacement on Dinitrolactone with NaI/Acetone.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone and 25 mL of 15% sodium iodide/acetone solution was stirred at room temperature for 15 h. TLC analysis, diethyl ether as the eluent, indicated only dinitrolactone present with an R_f value of 0.60. The reaction mixture was diluted with 0.5 mL of water and then heated at reflux for 3 h. TLC analysis showed no change. To the clear

orange solution was added 3.0 g of sodium iodide, and heating was continued for an additional 21 h. The clear orange solution was cooled to room temperature. The solid which formed was collected by suction to afford 0.35 g of dinitrolactone: mp 168-169°; mmp 169-170°; IR (3826) identical to that of starting material. The filtrate was cooled in an ice bath and a solid precipitated from solution. This was collected by suction to afford 0.15 g of dinitrolactone: mp 168-169°; mmp 168-170°; IR (3827) identical to that of the material above.

Attempted Nucleophilic Displacement on Dinitrolactone with KI in DMSO.

A 10-mL round-bottomed flask was charged with 0.20 g (0.00078 mol) of dinitrolactone, 3 mL of dry DMSO, and 0.50 g (0.0033 mol) of potassium iodide. The clear orange solution was stirred at room temperature for 24 h. TLC analysis, diethyl ether as the eluent, showed dinitrolactone, R_f value 0.60, as the only component in the reaction mixture. The orange liquid was heated at 110° for 24 h. TLC analysis after this time showed no change in the reaction mixture. The solution was cooled and diluted with 5 mL of water. A solid precipitated from the solution which was collected by suction, washed with water, and air-dried to afford 0.20 g (100% recovery) of

dinitrolactone: mp 169-170°; mmp 169-170°; IR (3824) identical to that of the starting material.

Ammonolysis of Monolactone to 2-(2-Hydroxyethoxy)-benzamide.

In a 15-mL round-bottomed flask was placed 0.52 g (0.0032 mol) of monolactone and 10 mL of 30% aqueous ammonium hydroxide. The heterogeneous mixture was stirred at room temperatrue for 2.5 h. After the first 10 min the reaction mixture became a clear, yellow solution. The water was removed by evaporation on a steam bath to afford 0.55 g (97%) of a yellow oil, which crystallized at room temperature. The solid was recrystallized twice from ethyl acetate/diethyl ether to afford 0.42 g (74%) of 2-(2-hydroxyethoxy)-benzamide: mp 112-113°; mmp 112-113°; IR (2815) and ^{1}H NMR (7417) (acetone) were identical to those of the material prepared from 2-(2-hydroxyethoxy)-benzoic acid, methyl ester.

Treatment of 2-(2-Hydroxyethoxy)-benzamide with Aqueous Ammonium Hydroxide.

A suspension of 0.30 g (0.00106 mol) of 2-(2-hydroxyethoxy)-benzamide and 25 mL of 30% ammonium hydroxide was stirred at room temperature for 0.5 h, with no effect. It was heated at reflux for 1 h with the complete dissolution of the solid. After the contents had been cooled in an

ice bath, a solid precipitated which was then collected by suction and air-dried to afford 0.30 g (100% recovery) of 2-(2-hydroxyethoxy)-benzamide: mp 112-113°; mmp 112-113°; IR (4784) identical to that of the starting material.

Preparation of the Spirocyclic Meisenheimer Complex from the Dinitrolactone.

A suspension of 0.50 g (0.00196 mol) of dinitrolactone and 5 mL of absolute methanol in a 10-mL round-bottomed flask was stirred for 5 min at room temperature and then treated with 0.28 g (0.00194 mol) of potassium thiophenolate dissolved in 1 mL of absolute methanol. The reaction mixture turned bright yellow immediately. It was stirred for 2 h at room temperature, solid being present at all times. The solid was collected by filtration and rinsed with methanol to afford 0.10 g of dinitrolactone: IR (4447) identical to that of the starting material. The clear yellow filtrate was stirred at room temperature for 2 h, during which time a yellow solid precipitated. The solid was collected by suction and rinsed with methanol to yield 0.455 g (90%) (Calculated from 0.40 g (0.0015 mol) of dinitrolactone) of the spirocyclic Meisenheimer complex: IR (4448), ^{1}H NMR (9475) (acetone), and ^{1}H NMR (9487) (DMSO) were identical to that of material prepared from 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester.

Preparation of the Spirocyclic Meisenheimer Complex from 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester.

A 25-mL round-bottomed flask was charged with 0.50 g (0.00177 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester and 5 mL of absolute methanol. To the clear yellow solution was added 0.29 g (0.00194 mol) of potassium thiophenolate dissolved in 1 mL of absolute methanol. The solution immediately changed to a clear red-orange. While it was stirred at ambient temperature for 4 h, a yellow solid formed. This was collected by suction, rinsed with 3 x 10 mL of methanol, and dried to yield 0.550 g (97%) of the spirocyclic Meisenheimer complex, which was recrystallized from methanol/water: 220° discolors, 230° decomposes: IR (4312) 3100 (alkene C-H stretching), 3000-2900 (aliphatic C-H stretching), 1690 (ester C=O), 1600 (C=C alkene), 1520, 1330 (nitro), 1300-1200 (C-O); ^{1}H NMR (6652) (DMSO) 8.5-8.0 (m, 2, alkene), 4.1 (s, 4, OCH_2CH_2O), 3.38 (s, 3, OCH_3); ^{13}C NMR (6653) (DMSO) 165.59, 129.04, 128.07, 125.66, 119.16, 116.30, 107.06, 69.28, 51.01; MS (520) 254 (100), 194 (69), 118 (34), 74 (38), 62 (70), 53 (31); UV (1250) (acetone) 388 (23,760), 475 (23,780).

Anal. Calcd for $C_{10}H_9N_2O_8K$ (324): C, 37.03; H, 2.79; N, 8.63. Found: C, 37.42; H, 2.67; N, 8.81.

Treatment of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester with KCN/Acetone/DMSO to produce the Spirocyclic Meisenheimer Complex.

A mixture of 7 mL of ultrapure acetone and 0.115 g (0.00177 mol) of potassium cyanide in a 25-mL round-bottomed flask was stirred at room temperature for 0.5 h, without complete dissolution of the solid. To this was added 0.5 mL of dry DMSO. To the clear solution was added 0.50 g (0.00177 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester. The deep red solution was stirred for 1.5 h at room temperature and then diluted with 20 mL of diethyl ether. The precipitated solid was collected by suction and rinsed several times with diethyl ether to afford 0.550 g (96%) of the spirocyclic Meisenheimer complex: IR (4258) were identical to those of material prepared from dinitrolactone.

Preparation of 2-Thiophenoxy-3,5-dinitrobenzoic Acid from the Spirocyclic Meisenheimer Complex.

A 10-mL round-bottomed flask was charged with 0.15 g (0.00047 mol) of spirocyclic Meisenheimer complex and 4 mL of absolute methanol. The yellow heterogeneous mixture was stirred at room temperature for 15 min and was then treated with 0.288 g (0.00194 mol) of potassium thiophenolate dissolved in 1 mL of absolute methanol. The reaction mixture turned orange in color immediately after

the addition of the potassium thiophenolate solution and within 5 min all solid material was dissolved. The clear orange solution was stirred at room temperature for 1 h and then heated to 50° for 15 min. This was chilled in an ice bath and treated with 5% aqueous hydrochloric acid until a solid precipitated from solution and the reaction solution tested acidic to pH paper. The solid was collected by suction, rinsed several times with ether and absolute methanol to yield 0.14 g (95%) of 2-thiophenoxy-3,5-dinitrobenzoic acid. The yellow solid was recrystallized once from ethanol/water: mp 202-203°; mmp 202-203°; ^{1}H NMR (9477) (acetone) was identical to that of material prepared from 2-chloro-3-5,dinitrobenzoic acid.

Preparation of the Spirocyclic Meisenheimer Complex from Dinitrolactone with KCN/Methanol.

A mixture of 0.12 g (0.00196 mol) of potassium cyanide dissolved in 5 mL of absolute methanol and 0.50 g (0.00196 mol) of dinitrolactone was placed in a 25-mL round-bottomed flask which contained 10 mL of absolute methanol. The clear red solution was stirred at room temperature for 5 min after which time a solid precipitated. This mixture was stirred at room temperature for an additional 15 min. The orange solid was collected by suction to afford 0.60 g (95%) of the spirocyclic Meisenheimer complex: IR (4362) and ^{1}H NMR

(9732) (DMSO) were identical to those of the material prepared from dinitrolactone and potassium thiophenolate.

Preparation of the Spirocyclic Meisenheimer Complex from 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester via KCN/Methanol.

A solution of 0.50 g (0.00174 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester, dissolved in 5 mL of absolute methanol, was added to a methanolic solution containing 0.11 g (0.0017 mol) of potassium cyanide, whereupon the mixture turned red immediately. After 5 min a solid precipitated. After stirring at room temperature had been maintained for an additional 0.5 h, the solid was collected by suction and rinsed several times with absolute methanol to afford 0.35 g (63%) of the spirocyclic Meisenheimer complex: IR (4727) and ^{1}H NMR (9733) (DMSO) were identical to those of the material prepared from the dinitrolactone.

Preparation of 2-Amino-3,5-dinitrobenzamide from the Spirocyclic Meisenheimer Complex.

A 0.15-g (0.00047 mol) sample of spirocyclic Meisenheimer complex and 5 mL of 30% aqueous ammonium hydroxide were placed into a 10-mL round-bottomed flask. The resulting heterogeneous mixture turned orange in color and was stirred for 15 min at room temperature with

incomplete dissolution of the solid. The mixture was gently heated to 50° until all solid was completely dissolved. The reaction temperature was maintained at 50° for an additional 10 min after complete dissolution. The resulting clear yellow solution was cooled in an ice bath, and a solid precipitated from the solution. The yellow solid was collected by suction to afford 0.10 g (94%) of crude product, which after one recrystallization from water afforded 2-amino-3,5-dinitrobenzamide: mp 280-282°; mmp 278-281°; IR (4509) and ^{1}H NMR (9480) (DMSO) were identical to those of material prepared from dinitrolactone.

Preparation of 3,5-Dinitrosalicylic Acid from the Spirocyclic Meisenheimer Complex.

A 10-mL round-bottomed flask was charged with 0.15 g (0.00047 mol) of the spirocyclic Meisenheimer complex and a 5-mL aqueous solution of 0.2 g (0.005 mol) sodium hydroxide. The resulting clear red solution was cooled and stirred at room temperature for 1 h. To the solution was added 0.5 mL of concentrated hydrochloric acid which caused the solution to become clear yellow followed by the formation of a solid. After cooling the mixture in an ice bath, the solid material was collected by suction and recrystallized once from water to yield 0.10 g (93%) of 3,5-dinitrosalicylic acid: mp 172-173°; mmp 172-174°; IR

(4513) was identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 2-Dimethylamino-3,5-dinitro-N,N-dimethylbenzamide from the Spirocyclic Meisenheimer Complex.

A mixture of 7 mL of aqueous 25% dimethylamine and 0.15 g (0.00047 mol) of the spirocyclic Meisenheimer complex was placed in a 10-mL round-bottomed flask. It turned orange in color; the solid dissolved within 5 min to afford a clear red solution which was stirred at room temperature for 12 h and then heated on a steam bath to concentrate the sample volume to 2 mL. The solid which precipitated was collected by suction to afford 0.12 g (90%) of 2-dimethylamino-3,5-dinitro-N,N-dimethylbenzamide which was recrystallized from ethanol/water: mp 105-106°; mmp 106-107°; IR (4512) and ^{1}H NMR (9485) (acetone) were identical to those of material prepared from dinitrolactone.

Treatment of Spirocyclic Meisenheimer Complex with Sodium Methoxide: Reflux Conditions.

A 25-mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was flame-dried and flushed with nitrogen. To the flask were added 6 mL of absolute methanol and 0.2 g of sodium metal. To the clear, cooled sodium methoxide solution was added 0.250 g

(0.00077 mol) of spirocyclic Meisenheimer complex. The orange suspension was stirred for 1 h at room temperature. A 1-mL aliquot was removed from the mixture; an orange solid was collected by suction and rinsed with methanol to afford 0.10 g of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex: IR (4403) identical to material prepared from 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester.

To the remaining orange suspension was added the methanolic filtrates from above. When the mixture was heated at reflux, it first became a clear red solution and then a yellow solid formed after 1 h. After a reflux period of 3 h, the solid was collected by suction to afford 0.125 g of 2-methoxy-3,5-dinitrobenzoic acid, sodium salt: IR (4413) identical to material prepared from 2-chloro-3,5-dinitrobenzoic acid. Treatment of the salt with 20% aqueous hydrochloric acid at 50° afforded 0.10 g of 2-methoxy-3,5-dinitrobenzoic acid: mp 164-165°; mmp 164-165°; IR (4378) identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

The methanolic filtrate was evaporated under reduced pressure to afford 0.05 g of a maroon solid: IR (5000) identical to material obtained from previous experiments.

Conversion of the Spirocyclic Meisenheimer Complex to the 2-Methoxy-2-(2-hydroxyethoxy)-Meisenheimer Complex.

A 25-mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was flame-dried and flushed with nitrogen. To the flask was added 6 mL of absolute methanol and 0.2 g of sodium metal. To the clear sodium methoxide solution was added 0.20 g (0.00617 mol) of the spirocyclic Meisenheimer complex. The orange-red mixture was stirred for 1 h at room temperature, after which time a 3-mL aliquot was removed from the reaction mixture. The solid was collected by suction to afford 0.10 g of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex: IR (4403) identical to that of material previously prepared from 3,5-dinitro-2-(2-hydroxyethoxy)-benzoic acid methyl ester.

The remaining mixture was diluted with 5 mL of absolute methanol and heated to reflux. After 0.5 h of heating, the reaction mixture became a clear red solution. After an additional 1 h of heating the formation of a solid was noted. This mixture was heated for an additional 1 h and then cooled to room temperature. The yellow solid was collected by suction and rinsed several times with absolute methanol to afford 0.125 g of the sodium salt of 2-methoxy-3,5-dinitrobenzoic acid: IR (4413) was identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

The filtrate was evaporated under reduced pressure to afford 0.050 g of a maroon solid: 105-110° decomposes; IR (4713) identical to that of material prepared from the dinitrolactone.

Treatment of the Spirocyclic Meisenheimer Complex with Absolute Methanol at Room Temperature and at Reflux.

In a 10-mL round-bottomed flask were placed 0.10 g (0.000309 mol) of the spirocyclic Meisenheimer complex and 5 mL of absolute methanol. The heterogeneous mixture was stirred at room temperature for 2 h. The solid was collected by suction and air-dried to afford 0.10 g of the spirocyclic Meisenheimer complex: IR (4720) identical to the starting material.

In a 10-mL round-bottomed flask was placed 0.10 g (0.000309 mol) of the spirocyclic Meisenheimer complex and 5 mL of absolute methanol. The heterogeneous mixture was stirred and heated at reflux for 1 h. The clear orange solution was cooled to room temperature with a solid present in the solution. The solid was collected by suction and air-dried to afford 0.10 g of spirocyclic Meisenheimer complex: IR (4722) identical to that of the starting material.

Spirocyclization of 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex in Acetone.

A 0.10-g (0.000294 mol) sample of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex was dissolved in 3 mL of dry acetone and stirred at room temperature for 0.5 h. The acetone was removed under reduced pressure, the solid was collected, recrystallized once from ethanol, and dried by means of a heat gun to afford 0.08 (84%) of the spirocyclic Meisenheimer complex: IR (4276) and ^{1}H NMR (9759) (DMSO) were identical to those of the material prepared from the reaction of dinitrolactone with potassium thiophenolate.

^{1}H NMR Study of the Spirocyclic Meisenheimer Complex in DMSO with Absolute Methanol Added.

A 0.250-g (0.00077 mol) sample of the spirocyclic Meisenheimer complex was dissolved in 1 mL of NMR-grade DMSO: ^{1}H NMR (9716) identical to that of material prepared from dintrolactone. To the orange solution was added 20 microliters (0.00078 mol) of absolute methanol. A ^{1}H NMR spectrum was recorded (9717) which was identical to previous ^{1}H NMR spectra of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex. See for example spectrum: ^{1}H NMR (9206) (DMSO).

Conversion of the 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex to the Spirocyclic Meisenheimer Complex by Treatment with Potassium Thiophenolate.

A 5-mL round-bottomed flask was charged with 0.15 g (0.00044 mol) of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex and 2 mL of absolute methanol. To the orange suspension was added 0.086 g (0.000582 mol) of potassium thiophenolate dissolved in 0.3 mL of absolute methanol. The reaction mixture was stirred at room temperature for 0.5 h during which time the solid totally dissolved in the yellow solution and a new yellow solid precipitated from the solution. The yellow solid was collected by suction, rinsed several times with absolute methanol, and recrystallized once from methanol to afford 0.12 g (84%) of spirocyclic Meisenheimer complex: IR (4749) and ^{1}H NMR (9758) (DMSO) were identical to those of the material prepared from the treatment of the dinitrolactone with potassium thiophenolate.

Preparation of 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex from 3,5-Dinitro-2-(2-hydroxyethoxy)-benzoic Acid Methyl Ester.

A 25-mL round-bottomed flask, equipped with a reflux condenser and magnetic stirring bar, was flame-dried and flushed with nitrogen. To the flask was added 15 mL of absolute methanol and 0.10 g of sodium metal. To the

clear sodium methoxide solution was added a solution of 0.50 g (0.000174 mol) of 3,5-dinitro-2-(2-hydroxyethoxy)-benzoic acid, methyl ester in 5 mL of absolute methanol. The reaction mixture turned orange, and within 2 min a solid had precipitated. The mixture was stirred for an additional 0.5 h at room temperature under nitrogen and then chilled in an ice bath. The orange solid was collected by suction, rinsed with absolute methanol, and recrystallized from ethanol (methanol/water also possible) to afford 0.55 g (94%) of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex: mp 192-193° discolors at 175°; IR (4363) 3650-3200 (alcohol OH), 3110 (alkene C-H stretching), 3000-2910 (aliphatic C-H stretching), 1690 (ester C=O), 1610 (alkene C=C stretching), 1530, 1330 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (9206) (DMSO) 8.5-8.0 (dd, 2, alkene), 4.2 (s, 4, OCH_2CH_2O), 3.7 (s, 3, OCH_3), 3.4 (s, 1, OH), 3.2 (s, 3, OCH_3); ^{13}C NMR (6571) (DMSO) 165.50, 128.95, 127.98, 125.57, 119.07, 116.21, 107.04, 69.19, 50.91, 48.44; MS (519) 254 (6), 194 (5), 44 (100); UV (2151) (acetone) 388 (22,300), 474.5 (22,350).

Anal. Calcd for $C_{11}H_{13}N_2O_9Na$ (3353): C, 38.83; H, 3.84; N, 8.23. Found: C, 38.62; H, 3.54; N, 8.50.

Preparation of the 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex from the Dinitrolactone.

A 25-mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was flame-dried and flushed with nitrogen. To the flask was added 15 mL of absolute methanol and 0.2 g of sodium metal. To the clear sodium methoxide solution was added 0.50 g (0.00196 mol) of dinitrolactone. The orange heterogeneous mixture was stirred for 1.5 h at room temperature under nitrogen. The solid was collected by suction, rinsed several times with absolute methanol, and recrystallized once from methanol to afford 0.60 g (91%) of the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex: mp 175° discolors, 192-193° melts; IR (4579) and ^{1}H NMR (9490) (DMSO) were identical to those of material prepared from 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester.

Treatment of Dinitrolactone with Excess Sodium Methoxide and Isolation of Intermediates to 2-Methoxy-3,5-dinitrobenzoic Acid.

A 25-mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was flame-dried and flushed with nitrogen. To the flask were added 6.0 mL of absolute methanol and 0.20 g of sodium metal. To the clear sodium methoxide solution was added 1.0 g (0.00393 mol) of purified dinitrolactone; the resulting heterogeneous

orange mixture was stirred at room temperature for 0.5 h. From the mixture was taken a 2-mL aliquot whose solid was collected by suction, rinsed with 3 x 2 mL of absolute methanol, and air-dried to afford 0.15 g of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex: IR (4377) identical to that of material prepared from 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester.

The remaining orange mixture was diluted with 5 mL of absolute methanol and heated at reflux for 3 h. During this time the solution cleared to a red solution which was later followed by the formation of a yellow solid. The yellow solid was collected by suction and rinsed with 3 x 5 mL of absolute methanol to afford 0.300 g of 2-methoxy-3,5-dinitrobenzoic acid, sodium salt: IR (4376) identical to that of material prepared from the reaction of 2-chloro-3,5-dinitrobenzoic acid with sodium methoxide.

This was dissolved in 5 mL of water and treated with 1 mL of concentrated sulfuric acid. The white precipitate was collected by suction, recrystallized from water, and air-dried to afford 0.20 g of 2-methoxy-3,5-dinitrobenzoic acid: mp 164-165°; mmp 164-165°; IR (4443) identical to that of the material prepared from 2-chloro-3,5-dinitrobenzoic acid.

The filtrate was evaporated under reduced pressure to afford a maroon solid, from which a 0.10-g sample was taken for spectral analysis: IR (4375) 3100 (aromatic or alkene C-H stretching), 3020-2820 (aliphatic C-H

stretching), 1700 (carbonyl), 1620 (C=C stretching), 1530, 1330 (nitro), 1300-1000 (C-O bend); UV (1277) (acetone) 386.5, 471.5, and (1365) (methanol) 346. The remaining maroon solid was dissolved in 5 mL of water and treated with 2 mL of 3 M aqueous hydrochloric acid. A solid precipitated from the reaction mixture which afford 0.60 g of a white solid. This was recrystallized once from methanol/water and once from water to afford 2-methoxy-3,5-dinitrobenzoic acid: mp 163-164°; mmp 163-165°; IR (4378), ^{1}H NMR (8789) (acetone), ^{13}C NMR (6247) (acetone) and MS (450) were all identical to those of the material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 2-Methoxy-3,5-dinitrobenzoate Acid, Sodium Salt from 2-Chloro-3,5-dinitrobenzoic Acid.

A mixture of 1.0 g (0.0040 mol) of 2-chloro-3,5-dinitrobenzoic acid and 0.35 g (0.00875 mol) of sodium hydroxide dissolved in 4 mL of absolute methanol was stirred at room temperature. After 10 min an orange-yellow solid precipitated from the clear red solution. The mixture was stirred for an additional 1 h at room temperature, after which time the solid was collected by suction, rinsed several times with methanol, and air-dried to afford 1.0 g (93%) of the sodium salt of 2-methoxy-3,5-dinitrobenzoic acid as a yellow powder: IR (4425) 3100 (aromatic C-H stretching), 1640, 1400 (asymmetric and

symmetric stretch of carboxylate), 1560, 1350 (nitro), 1300-1000 (C-O bend).

The same result was obtained when sodium methoxide was generated from sodium metal and absolute methanol. The yield of the salt was 93%: IR (4427) was identical to the IR above (4425).

Acidification of 2-Methoxy-3,5-dinitrobenzoic Acid, Sodium Salt from 2-Chloro-3,5-dinitrobenzoic Acid.

A 0.30-g (0.00113 mol) sample of the sodium salt from above was dissolved in 10 mL of water and treated with concentrated hydrochloric acid to afford 0.25 g (91%) of 2-methoxy-3,5-dinitrobenzoic acid, which was recrystallized twice from methanol/water: mp 164-165°; mmp 164-165°; IR (4441) identical to that of material previously prepared from 2-chloro-3,5-dinitrobenzoic acid.

Sequential Treatment of Methoxy lactone Meisenheimer Complex with Sodium Methoxide and Aqueous Acid.

A 0.20-g sample of methoxy lactone Meisenheimer complex was treated with pregenerated sodium methoxide in absolute methanol and heated at reflux for 10 min. The clear red solution was concentrated under reduced pressure and treated with 10 mL of 10% aqueous hydrochloric acid. A solid which precipitated from the solution was collected by suction. This was recrystallized once from water and

air-dried to afford 0.12 g of 2-methoxy-3,5-dinitrobenzoic acid: mp 164-165°; mmp 164-165°; IR (4715) identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Treatment of 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex with Sodium Methoxide: Reflux Conditions.

A 25-mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was flame-dried and flushed with nitrogen. To the flask were added 15 mL of absolute methanol and 0.20 g of sodium metal. To the clear cooled sodium methoxide solution was added 0.25 g (0.00073 mol) of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex. The resulting mixture was heated to reflux for 1 h, during which time the solution became homogeneous. The clear red solution was cooled and filtered, and the methanol was removed from the filtrate under reduced pressure. A maroon solid was collected: IR (4714) identical to that of material prepared in the same manner. The maroon solid was treated with 15 mL of 10% aqueous hydrochloric acid. An off-white solid formed in the solution, which was collected by suction, recrystallized once from water and air-dried to afford 0.15 g (88%) of 2-methoxy-3,5-dinitrobenzoic acid: mp 164-165°; mmp 164-165°; IR (4713) identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 3,5-Dinitrosalicylic Acid from the 2-Methoxy 2-(2-hydroxyethoxy) Meisenheimer Complex.

A 10-mL round-bottomed flask was charged with 0.20 g (0.00058 mol) of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex and 5 mL of an aqueous solution containing 0.20 g (0.0050 mol) of sodium hydroxide. The reaction mixture, which darkened immediately to a red color, was stirred for 1.5 h at room temperature. After this time, not all of the solid complex had dissolved; heat was applied to the reaction mixture until the temperature of the solution was 60°. Heating was continued for 10 min after the complete dissolution of the solid. The deep red solution was chilled in an ice bath and acidified with concentrated hydrochloric acid. From this solution precipitated a yellow solid which was collected by suction and air-dried to yield 0.14 g of a bright yellow salt: IR (4523) was identical to that of the sodium salt of 3,5-dinitrosalicyclic acid.

A 0.13-g sample of the yellow salt from above was placed in 3 mL of water and treated with 1 mL of concentrated sulfuric acid. A white solid was collected and recrystallized once from water to afford 0.11 g (95%) of 3,5-dinitrosalicyclic acid: mp 171-172°; mmp 171-172°; IR (4524) was identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 2-Thiophenoxy-3,5-dinitrobenzoic Acid from the 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex.

To a suspension of 0.20 g (0.00058 mol) of the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex in 1 mL of absolute methanol was added 1 mL of methanolic 0.00194 molar potassium thiophenolate. The orange-red suspension was stirred at room temperature for 0.5 h and then heated to 50° for 0.5 h until all solid had dissolved. The clear orange solution was cooled in an ice bath and acidified with 5% aqueous hydrochloric acid until a solid precipitated from the solution. The solid was collected by suction and then recrystallized once from ethanol/water to afford 0.15 g (85%) of 2-thiophenoxy-3,5-dinitrobenzoic acid: mp 200-202°; mmp 200-202°; IR (4521) and ^{1}H NMR (9478) (acetone) were identical to those of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 2-Amino-3,5-dinitrobenzamide from the 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex.

A mixture of 0.20 g (0.00058 mol) of the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex and 5 mL of 30% aqueous ammonium hydroxide was stirred for 1 h at room temperature. It turned orange and still contained solid. The mixture was heated to 60° until all the solid had dissolved and then an additional 5 min, until a solid began to precipitate. The mixture was cooled in an ice

bath and a bright yellow solid was collected by suction. After one recrystallization from water, 0.10 g (85%) of 2-amino-3,5-dinitrobenzamide was obtained: mp 280-282°; mmp 279-281°; IR (4522) and ^{1}H NMR (9481) (DMSO) were identical to those of material prepared from dinitrolactone.

Preparation of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester from the Spirocyclic Meisenheimer Complex.

In a 25-mL round-bottomed flask was placed 0.15 g (0.00047 mol) of spirocyclic Meisenheimer complex and 10 mL of 10% aqueous hydrochloric acid. The mixture was stirred at room temperature for 0.5 h with no apparent dissolution of the solid. The mixture was heated to 40° for 5 min at which point complete dissolution occurred. The clear solution was cooled in an ice bath and extracted with 3 x 15 mL of methylene chloride. The organic layers were combined and washed with 10 mL of cold dilute sodium bicarbonate followed by 1 x 15 mL of water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford 0.12 g (90%) of a yellow liquid identified as 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester: IR (4496) and ^{1}H NMR (9456) (DMSO) were identical to those of material prepared from the transesterification of dinitrolactone.

Aqueous Acid Hydrolysis of the 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex.

A 25-mL round-bottomed flask was charged with 10 mL of 20% aqueous hydrochloric acid and 0.20 g (0.00588 mol) of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex. The heterogeneous mixture was stirred at room temperature for 1 h with no apparent change. The mixture was heated to 50° until all the solid material had dissolved. The solution was chilled immediately after complete dissolution of the solid and was extracted with 3 x 20 mL of methylene chloride. The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford 0.15 g (90%) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester: IR (4365) and ^1H NMR (9355) ($CDCl_3$) were identical to those of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester.

Nucleophilic Displacement on Dinitrolactone with 1,6-Diaminohexane. Formation of Zwitterionic Meisenheimer Complex.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone and a 25-mL aqueous solution containing 0.25 g (0.0021 mol) of 1,6-diaminohexane was stirred at room temperature for 0.5 h. The resulting clear yellow solution was heated to boiling for 5 min and then cooled in an ice bath. An orange solid which precipitated was collected by suction

and rinsed with cold water to afford 0.40 g (60%) of the zwitterionic Meisenheimer complex: mp 208-215°; IR (3635) 3600-3200 (alcohol OH), 3500-2500 (ammonium salt), 1600 (carboxylic salt C=O), 1520, 1320 (nitro); ^{1}H NMR (8658) (DMSO) 8.8-8.4 (dd, 2, alkene), 3.9-3.6, 3.0-2.6, 1.8-1.0 (m, 18, CH_2, OH, NH_2^+, and NH_3^+); ^{13}C NMR (7048) (DMSO) 167.93, 167.61, 149.27, 133.86, 132.75, 129.63, 124.85, 45.67, 28.96, 26.94, 26.75, 25.84, 25.45; MS (552) no fragmentation observed; UV (1299) (acetone) 371.5 (14,100).

Anal. Calcd for $C_{13}H_{20}N_4O_7$ (344): C, 45.34; H, 5.81; N, 16.27. Found: C, 44.98; H, 5.58; N, 15.99.

UV Study of 3,5-Dinitrosalicylic Acid/Acetone with Various Bases.

A solution of 0.088 g (0.000039 mol) of 3,5-dinitrosalicylic acid in 3 mL of acetone was treated with varying amounts of 1,6-diaminohexane dissolved in acetone. UV (1307) (acetone) of 3,5-dinitrosalicylic acid showed no absorption above 330. After addition of 1,6-diaminohexane: (1308) 358.5, (1 equivalent); (1309) 358.5, (2 equivalents); (1310) 359, (excess 1,6-diaminohexane).

A similar experiment was done where a solution of sodium hydroxide dissolved in acetone was used: UV (1312) 359, (2 equivalents of base).

When triethylamine was used as the base, an identical UV spectrum was obtained: UV (1313) 358.5, (excess base).

Attempted Nucleophilic Displacement on Dinitrolactone with KCN under various conditions.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone and 0.50 g (0.0077 mol) of potassium cyanide was dissolved in 15 mL of ultrapure acetone. The reaction mixture, which immediately turned purple at room temperature, was stirred at room temperature and examined by TLC analysis, diethyl ether as the eluent, which showed dinitrolactone as the sole component in the reaction mixture. To the solution was added 0.25 mL of water. After 0.5 h, TLC analysis showed, visibly, three new components in the reaction mixture with R_f values of 0.40, 0.20, and baseline tarring. The component with an R_f value of 0.40 was purple, and the component with an R_f value of 0.20 was yellow. After 1 h, TLC analysis indicated that the dinitrolactone was almost completely gone from the reaction mixture and the baseline tar was becoming more intense. The dark mixture was poured onto a fritted glass column packed with 50 g of Baker silica gel 7 and eluted with 300 mL of diethyl ether. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to afford 0.30 g of a red oil: IR (3810) 3600-3000 (alcohol OH), 2240 (nitrile), 1740 (ester C=O), 1550, 1350 (nitro),

1300-1000 (C-O bend). Attempted purification by preparative TLC afforded intractable tars. No further experimentation was pursued. Experimental results to be noted are as follows. Dinitrolactone produced a purple color in DMSO or acetone or a mixture of DMSO or acetone when treated with potassium cyanide. [2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester forms the spirocyclic Meisenheimer complex when treated with potassium cyanide in acetone.] No reaction appeared to occur with the dinitrolactone until the addition of water. However, with the addition of water, a black intractable tar was obtained along with a purple red solution. Attempts to purify this by column chromatography and preparative TLC failed.

Experiments showed that acidification of the purple filtrates (after partial purification with a silica plug as described previously) led to dark intractable oils.

Experiments conducted at -78° and -40° with dry acetone and acetonitrile, respectively, dinitrolactone, and potassium cyanide afforded quantitative recovery of the dinitrolactone. In a typical experiment, a solution containing one equivalent of potassium cyanide was added to a solution containing one equivalent of the dinitrolactone. The mixture was stirred at room temperature for 0.5 h until the solids were dissolved and then filtered. The purple filtrate would then be cooled to either -78° or -40°, depending on the solvent, and

stirred for several hours at the respective temperature. Solid, which precipitated after several hours, was shown to be dinitrolactone. The filtrate was then treated with water, which forced out the remaining dinitrolactone. In both of these cases, no dark tarry byproducts were obtained.

Spectral analysis of the noted purple solution by ^{1}H NMR (9699-9701) (DMSO) (acetone too insoluble) showed that additon of 1.1 equivalents of potassium cyanide to the solution of dinitrolactone produced only slight changes in the ^{1}H NMR. Addition of excess potassium cyanide, however, destroyed all material and a black suspension was found in the ^{1}H NMR tube. Treatment of dinitrolactone dissolved in acetone with an equivalent of solid potassium cyanide produced UV absorptions at 505 and 374.5, indicative of a Meisenheimer complex.

Treatment of Dinitrolactone with Trimethylsilyl cyanide.

In a flame-dried 25-mL round-bottomed flask were placed 0.50 g (0.00196 mol) of dinitrolactone and 0.26 mL (0.0021 mol) of trimethylsilyl cyanide. The heterogeneous mixture was stirred at room temperature with no effect. The reaction was monitored by TLC analysis, diethyl ether as the eluent. To the heterogeneous mixture was added 3 mL of dry methylene chloride. The contents of the flask

were stirred for 1.5 h at room temperature, with TLC analysis showing no reaction occurring.

After 3.5 h, 3 mL of dry DMSO were added to the heterogeneous mixture and stirring of the solution was continued at room temperature. After 1.5 h, TLC analysis indicated no change in the reaction mixture. At this time a catalytic amount of potassium cyanide was added to the mixture, which was stirred for 1.5 h at room temperature; TLC analysis indicated no change in the reaction mixture.

The reaction was heated to 45° for 1.5 h. TLC analysis indicated no change. The mixture was cooled and diluted with 40 mL of water. The two-phase system was extracted with 3 x 30 mL of methylene chloride. The organic fractions were combined, dried ($MgSO_4$), and concentrated under reduced pressure to afford 0.45 g (90% recovery) of dinitrolactone: mp 169-170°; mmp 168-171°. No further experimentation was pursued.

Treatment of Dinitrolactone with Trimethylsilyl cyanide/18-Cr-6/KCN in Acetonitrile.

A 25-mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was flame-dried and flushed with nitrogen. To the flask were added 0.50 g (0.00196 mol) of dinitrolactone, a catalytic amount of 18-Cr-6-KCN, and 12 mL of dry acetonitrile. To the clear yellow solution was added 0.3 mL (0.0022 mol) of

trimethylsilyl cyanide which caused the solution to turn purple. The reaction mixture was stirred at room temperature. After 4 h, TLC analysis, diethyl ether as the eluent, showed dinitrolactone as the sole component in the reaction mixture. To the solution was added 0.50 g of potassium cyanide. TLC analysis, 16 h after the addition of potassium cyanide, showed dinitrolactone and baseline tar. To the solution was added 0.75 mL of trimethylsilyl chloride which caused the solution to darken. One hour after the addition of the trimethylsilyl chloride, TLC analysis showed baseline tar as the sole reaction component. Twenty mL of water was added to the mixture, which forced an intractable tar out of the solution. No further experimentation was pursued.

Treatment of Dinitrolactone with Potassium Cyanide/Dry DMSO and TMSCl.

A nitrogen flushed 10-mL round-bottomed flask was charged with 0.50 g (0.00196 mol) of dinitrolactone, 5 mL of dry DMSO, and 0.15 g (0.0023 mol) of potassium cyanide. To the clear purple solution was added 2 mL of trimethylsilyl chloride after which the system was flushed again with nitrogen. The reaction mixture became hot and turned dark. Monitoring of the reaction mixture by TLC, diethyl ether as the eluent, showed the slow disappearance of the dinitrolactone and the appearance of a new

material, R_f value of 0.20, over a 1-week period. Attempts to force the material out of solution with diethyl ether and hexane were unsuccessful. Addition of 15 mL of cold water forced out a tan substance from the reaction mixture. This was collected by suction and air-dried to afford 0.40 g of an unknown material: mp 209° decomposes, 224° becomes a black oil; IR (4338) 3100 (aromatic C-H stretching), 3060-3000 (aliphatic C-H stretching), 2240 (nitrile), 1700 (carbonyl), 1620 (aromatic C=C stretching), 1560, 1340 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (9932) (DMSO) 8.8-8.0 (d, aromatic), 4.9-4.6 (m, aliphatic), 3.5 (s, ?); ^{13}C NMR (7186) (DMSO) 165.66, 159.15, 140.49, 132.68, 130.54, 129.37, 120.46, 114.35, 112.07, 72.40, 66.29.

Attempted Nucleophilc Attack on the Dinitrolactone by the Enolate of Cyanoacetic Acid, Ethyl Ester.

A 25-mL round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, was flame-dried and flushed with nitrogen. To the flask was added 0.17 g (0.00425 mol) of 60% sodium hydride (mineral oil dispersion), which had been washed with 3 x 8 mL of dry hexane. To the sodium hydride was added 5 mL of dried DMSO (CaH_2) which was then heated to 65° for 1 h. Evolution of hydrogen gas was noted. To the resulting clear grey-yellow solution was added 0.5 mL (0.0044 mol)

of ethyl cyanoacetate; the clear yellow solution was cooled to room temperature. To the solution was added 1.0 g (0.00394 mol) of dinitrolactone dissolved in 5 mL of dry DMSO, whereupon the solution turned magenta. The solution was stirred for several hours at room temperature. TLC analysis, diethyl ether as the eluent, showed only starting material and baseline tarring. The reaction mixture was heated to 65-70^{o} for 24 h. TLC analysis indicated the existence of starting material and baseline tarring. The mixture was cooled to room temperature and added to 50 mL of saturated ammonium chloride and 8 drops of concentrated hydrochloric acid. The aqueous solution was extracted with 1 x 30 mL of diethyl ether and 2 x 30 mL of methylene chloride. The organic extracts were combined, washed with 50 mL of saturated aqueous sodium chloride, 50 mL of water, dried ($MgSO_4$), and concentrated under reduced pressure to afford 1.3 g of a dark brown oil: IR and ^{1}H NMR showed no tangible material.

A similar result was obtained when 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester was treated in the same manner. Again, starting material was present at all times by TLC analysis. Spectral analysis after an identical workup procedure afford these results: IR (4250) 3600-3400 (alcohol OH), 3100 (aromatic C-H stretching), 3000-2900 (aliphatic C-H stretching), 2240 (nitrile), 1760 (carbonyl), 1620, 1600 (aromatic C=C

stretching), 1550, 1350 (nitro), 1300-1000 (C-O bend). No further experimentation was pursued.

Treatment of the Dinitrolactone with 1,3-Diphenyl-2-propanone/Triethylamine/DMSO.

A suspension of 0.50 g (0.00196 mol) of dinitrolactone in a preformed solution of 0.42 g (0.0020 mol) of 1,3-diphenyl-2-propanone and 3 mL of triethylamine was stirred at room temperature for 1 h with no apparent change. Addition of 0.5 mL of dry DMSO (the minimum amount needed to dissolve all the solid material) resulted in a purple solution: UV (1355) (acetone) 373, 468.

Treatment of the purple solution with anhydrous diethyl ether caused the purple color to dissipate and dinitrolactone, 0.48 g (96% recovery), to precipitate from solution: mp 169-170°; mmp 168-170°. Variation in the amounts of ketone, amine, and anhydrous diethyl ether all resulted in the recovery of dinitrolactone. The use of toluene and cyclohexane in place of diethyl ether led to the same result.

Treatment of the Dinitrolactone with Ethyl Cyanoacetate/Triethylamine/DMSO.

A mixture of 3 mL of ethyl cyanoacetate and 0.5 mL of triethylamine was stirred at room temperature for 0.5 h. To the clear liquid was added 0.50 g (0.00196 mol) of

dinitrolactone. The white suspension was stirred at room temperature for 1 h with no apparent effect. To the suspension was added 0.5 mL of dry DMSO. (This was the minimum amount needed to dissolve all the solid material.) A purple solution resulted after the addition of the DMSO: UV (1354) (acetone) 474.5.

Treatment of the purple solution with anhydrous diethyl ether caused the purple color to dissipate and dinitrolactone to precipitate from solution: mp 169-170°; mmp 169-170°. Variation in the amounts of ethyl cyanoacetate, triethylamine, and anhydrous diethyl ether all resulted in the recovery of dinitrolactone. The use of toluene and cyclohexane in place of diethyl ether afforded the same result.

Treatment of Dinitrolactone with the Sodium Enolate of Acetone.

A solution of 3 mL of ultrapure dry acetone (stored over 4 A sieves) and 1.4 mL of 1.5 M sodium methoxide/methanol was stirred at room temperature for 1 h. To the solution was added 0.50 g (0.00196 mol) of dinitrolactone. The reaction mixture cleared to an orange solution. After 10 min a solid precipitated from the solution; stirring was continued for an additional 2 h at room temperature. The solid was collected by suction, rinsed several times with diethyl ether, and air-dried to

afford 0.62 g (94%) of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex: IR (5009) was identical to that of material prepared from treatment of dinitrolactone with sodium methoxide.

Treatment of Dinitrolactone with the Sodium Enolate of Dimethyl Malonate.

A solution of 3 mL of dimethyl malonate and 1.4 mL of 1.5 M sodium methoxide in methanol was stirred at room temperature for 0.5 h. To the solution was added 0.50 g (0.00196 mol) of dinitrolactone. The mixture quickly cleared to an orange solution. After 0.5 h a solid precipitated from the solution. This was collected by suction, rinsed several times with diethyl ether, and air-dried to afford 0.60 g of 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex: IR (5026) and UV (1364) (acetone) 388.5 (22,500), 474.5 (22,600) were identical to those of material prepared from treatment of dinitrolactone with sodium methoxide.

Attempted Nucleophilic Displacement with Potassium Thiocyanate on Dinitrolactone in Ethanol.

A mixture of 0.50 g (0.00196 mol) of dinitrolactone, 25 mL of 95% ethanol, and 2 g (0.020 mol) of KSCN in a 50-mL round-bottomed flask was heated to reflux, with complete dissolution of the solids. Refluxing was

continued for 24 h. The clear yellow solution was then chilled in an ice bath, with formation of a solid precipitate which was collected by suction to afford 0.50 g (100%) of dinitrolactone: mp 169-170°; mmp 169-170°; IR (4001) identical to dinitrolactone.

Experiments were conducted where the dinitrolactone was treated with various amounts of KSCN, ethanol, water, heat and length of reaction time. In each case, dinitrolactone was the sole isolated material.

Attempted Nucleophilic Displacement on Dinitrolactone with NH_4SCN in THF.

A 25-mL round-bottomed flask was charged with 0.50 g (0.00196 mol) of dinitrolactone, 1.0 g (0.013 mol) of NH_4SCN, and 15 mL of freshly distilled THF. The reaction mixture was stirred at room temperature for 1 h and then heated at reflux for 2 h. Water was added to the hot solution and a solid precipitated. The mixture was cooled in an ice bath; the solid was collected by suction and air-dried to afford 0.50 g (100%) of recovered dinitrolactone: mp 169-170°; mmp 169-170°.

Preparation of the Potassium Salt of 3,5-Dinitrosalicylic Acid, 2-Thiocyanatoethyl Ester.

A 15-mL round-bottomed flask, equipped with a reflux condenser and thermometer, was charged with 0.75 g

(0.00295 mol) of dinitrolactone, 1.5 g (0.015 mol) of potassium thiocyanate, and 5.5 mL of dry dimethyl sulfoxide. The reaction flask was flushed with a stream of nitrogen, and the heterogeneous yellow mixture was heated at 110° for 3 h. The reaction mixture became a clear yellow solution after a short while of heating and slowly changed color to a clear orange solution. TLC information, diethyl ether as the eluent, showed no starting material after 1.5 h.

After 3 h, the orange solution was poured slowly with vigorous stirring into a 100-mL beaker containing 25 g of crushed ice. A bright yellow solid formed immediately. The mixture was placed in a refrigerator for 12 h. The yellow solid was collected by suction to afford 1.0 g (97%) of product. After one recrystallization from ethanol/water, the product was obtained as a fine yellow powder: mp 270° darkened, decomposes violently at 340°; IR (4111) 3600-3400 (water), 3100 (C-H alkene), 2170 (SCN), 1725 (lactone C=O), 1600 (C=C alkene), 1560, 1340 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (9321) (DMSO) 8.6-8.4 (dd, 2, alkene), 4.6-4.3 (m, 2, $-CH_2O-$), 3.6-3.3 (m, 2, $-CH_2O-$); ^{13}C NMR (6664) (DMSO) 167.06, 164.59, 140.33, 131.16, 125.44, 122.71, 112.76, 61.84, 32.45; UV (1191) (methanol) 243 (16,100), 265 (16,400), 365 (16,500).

Anal. Calcd for $C_{10}H_6KN_3O_7S$ 0.5 H_2O (360): C, 33.33; H, 1.94; N, 11.65. Found: C, 32.98; H, 1.65; N, 11.26.

It is very important to use dry DMSO in this reaction. When DMSO/water 3:1 v:v was used as the solvent, an unidentifiable product was obtained in good yield, 0.60 g: mp 265°; IR (4113) 3100 (aromatic C-H stretching), 1710 (carbonyl), 1550, 1350 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (9124) (DMSO) 8.8 (s, aromatic); ^{13}C NMR (6514) (DMSO) 169.14, 166.54, 138.71, 130.12, 125.57, 120.11.

Anal. C, 30.81; H, 1.07; N, 11.17.

Treatment of the solid dissolved in DMSO with excess methyl iodide at room temperature afforded only the same material. No further experimentation was pursued.

Preparation of 3,5-Dinitrosalicylic Acid, 2-Thiocyanato-ethyl Ester.

Method A.

A 0.25-g (0.000712 mol) sample of the potassium salt of 3,5-dinitrosalicylic acid, 2-thiocyanatoethyl ester was dissolved in 25 mL of hot water in an Erlenmeyer flask. To the clear yellow solution was added 2 drops of concentrated hydrochloric acid. The solution turned milky white and then cleared; an off-white solid had precipitated from the solution. The pH of the aqueous solution was approximately 2 (indicator paper). After the flask had been chilled in an ice bath the solid was collected by suction to yield 0.22 g of a crystalline

material. One recrystallization from acetone/water afforded 0.20 g (91%) of a yellow-white, crystalline compound identified as 3,5-dinitrosalicylic acid, 2-thiocyanatoethyl ester: mp 139-140°;IR (4577) 3100 (aromatic C-H stretching), 2900 (aliphatic C-H stretching), 2160 (thiocyanate), 1690 (ester C=O), 1625, 1600 (C=C aromatic), 1545, 1360 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (9578) (DMSO) 8.9-8.8 (m, 2, aromatic), 4.9 (s, 1.2, OH, H_2O), 4.8-4.6 (m, 2, $-OCH_2-$), 3.6-3.4 (m, 2, $-CH_2O-$); ^{13}C NMR (6793) (DMSO) 164.81, 157.59, 138.73, 137.11, 129.89, 125.47, 118.70, 113.11, 64.47, 32.28; MS (498) 313 (5), 255 (3), 108 (50), 86 (100); UV (1192) (methanol) 209.5 (19,000), 281 (4600), 358.5 (11,200).

Anal. Calcd for $C_{10}H_7N_3O_7S$ (313): C, 38.34; H, 2.24; N, 13.41. Found: C, 38.36; H, 2.21; N, 13.49.

Preparation of 3,5-Dinitrosalicylic Acid, 2-Thiocyanatoethyl Ester.

Method B.

A 30-mL aliquot of 20% aqueous hydrochloric acid was poured into a 50-mL round-bottomed flask containing 0.20 g (0.000569 mol) of the potassium salt of 3,5-dinitrosalicylic acid, 2-thiocyanatoethyl ester. The heterogeneous mixture was stirred at room temperature for several minutes with no apparent change and then heated at reflux for 20 min. At no time did all of the solid

material dissolve. The hot mixture was filtered by gravity, and the filtrate was placed in an ice bath; a solid precipitated within a few minutes. It was collected by suction and air-dried to afford 0.05 g of an off-white solid (A): mp 135-137°; mmp 135-137°; IR (4539) was identical to that of material prepared by method A.

The solid collected by gravity filtration was treated with 20 mL of water and isolated by suction. When dried, the material (B) weighed 0.10 g: mp 136-137°. Mixture mp of A and B 136-137°. Both solids were combined and recrystallized from acetone/water: mp 138-139°; mmp 139-140°.

Preparation of 3,5-Dinitrosalicylic Acid from the Potassium Salt of 3,5-Dinitrosalicylic Acid, 2-Thiocyanatoethyl Ester: Acid Hydrolysis.

A 0.25-g (0.0007123 mol) sample of purified potassium salt of 3,5-dinitrosalicylic acid, 2-thiocyanatoethyl ester was dissolved in 12 mL of warm water and heated to reflux. To the clear yellow solution was added 1 mL of concentrated hydrochloric acid. The solution turned milky white followed by formation of a solid. The heterogeneous mixture was heated at reflux for 4 h, during which a solid was present at all times. The reaction mixture was filtered while hot; an off white solid, A, was collected and air-dried. The filtrate was saved and chilled in an

ice bath which afforded a second solid, B, which was collected by suction and air-dried.

Solid A, 0.05 g, was identified as the 3,5-dinitrosalicylic acid, 2-thiocyanatoethyl ester: mp 139-140°; mmp 139-140°. Solid B, 0.10 g (63%), was identified as 3,5-dinitrosalicylic acid: mp 169-170°; mmp 169-172°; IR (4652) was identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Preparation of 3,5-Dinitrosalicylic Acid from the Potassium Salt of 3,5-Dinitrosalicylic Acid, 2-Thiocyanatoethyl Ester: Base Hydrolysis.

A 0.25 g (0.0007123 mol) sample of the purified potassium salt of 3,5-dinitrosalicylic acid, 2-thiocyanatoethyl ester was treated with a solution of 0.1 g potassium hydroxide dissolved in 10 mL of water. The clear yellow solution was heated gently to 80° for 15 min and then cooled to room temperature. The clear yellow solution was extracted with 1 x 30 mL of diethyl ether; the aqueous layer was treated with concentrated sulfuric acid until the solution was acidic towards pH paper. A white solid precipitated from the solution; it was collected by suction and air-dried to yield 0.15 g (94%) of 3,5-dinitrosalicylic acid: mp 170-171°; mmp 169-170°; IR (4653) was identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Aqueous Acid Hydrolysis of 3,5-Dinitrosalicylic Acid, 2-Thiocyanatoethyl Ester.

In a 25-mL round-bottomed flask were placed 0.50 g (0.0016 mol) of 3,5-dinitrosalicylic acid, 2-thiocyanatoethyl ester and 10 mL of 20% aqueous sulfuric acid which was heated at reflux for 3 h. The solution was cooled in an ice bath with formation of a solid. It was collected by suction, to afford 0.32 g (88%) of dinitrosalicylic acid: mp 171-173°; mmp 171-172°.

Preparation of 2-Methoxy-3,5-dinitrobenzoic Acid, Methyl Ester via the Brewster/Ciotti Method.

A 1.0-g (0.00413 mol) sample of purified 2-methoxy-3,5-dinitrobenzoic acid dissolved in 20 mL of pyridine was treated with 1.57 g (0.00816 mol) of p-toluenesulfonyl chloride, whereupon the reaction mixture warmed to 30°. The clear orange solution was then chilled in an ice bath for 15 min, after which time 0.20 mL of absolute methanol was added. Stirring was maintained for 1 h at 0-5°, and then the solution was poured into 80 mL of ice/water. The oily suspension was stirred and scratched manually to yield a yellow solid, which was collected by suction and air-dried to afford 1.0 g (95%) of 2-methoxy-3,5-dinitrobenzoic acid, methyl ester. The material was recrystallized twice from ethanol/water to afford 0.90 g (86%) of the purified ester: mp 55-56° (lit[154] 69°), IR

(4647) 3100 (aromatic C-H stretching), 2980-2900 (aliphatic C-H stretching), 1740 (ester C=O), 1620, 1590 (aromatic C=C stretching), 1550-1530, 1350 (nitro), 1300-1000 (C-O bend); ^{1}H NMR (9610) (acetone) 8.9-8.8 (m, 2, aromatic), 4.1 (s, 3, OCH_3), 3.9 (s, 3, OCH_3); ^{13}C NMR (6828) (acetone) 163.94, 157.96, 145.86, 143.06, 130.58, 128.50, 124.20, 65.16, 53.71; MS (509) 256 (3), 194 (100), 75 (35); UV (1193) (MeOH) 213.5 (20,100), 269.0 (8165).

Anal. Calcd for $C_9H_8N_2O_7$ (256): C, 42.20; H, 3.15; N, 10.94. Found: C, 42.22; H, 3.00; N, 10.94.

Preparation of 3,5-Dinitrosalicylic Acid, Methyl Ester via the Brewster/Ciotti Method.

A mixture of 0.50 g (0.00219 mol) of 3,5-dinitrosalicylic acid, 20 mL of pyridine, and 0.9 g (0.0047 mol) of p-toluenesulfonyl chloride was chilled in an ice bath. To this was added 0.1 mL of absolute methanol. The clear yellow liquid was stirred at 0-5° for 1.5 h, then poured into 80 mL of ice/water. The oily suspension that formed crystallized upon standing. The shiny yellow prisms were collected by suction, rinsed with water, and recrystallized once from ethanol to afford 0.4 g (75%) of 3,5-dinitrosalicylic acid, methyl ester: mp 125-126° (lit[155] 124-128°); mmp 124-126°; IR (4762) 3500-2900 (phenol OH), 3100 (aromatic C-H stretching), 1700 (ester C=O), 1610 (aromatic C-H stretching), 1560, 1370

(nitro), 1300-1000 (C-O bend); ^{1}H NMR (9772) (acetone) 9.1-8.9 (dd, 2, aromatic), 4.15 (s, 3, OCH_3), no phenolic OH observed; ^{13}C NMR (6898) (acetone) 168.96, 159.66, 139.76, 139.44, 130.40, 126.89, 117.20, 54.44; MS (543) 242 (100), 210 (55), 152 (35), 78 (15), 62 (55); UV (1266) (MeOH) 217 (10,200), 363 (16,100).

Anal. Calcd for $C_8H_6N_2O_7$ (242): C, 39.68; H, 2.50; N, 11.57. Found: C, 39.98; H, 2.44; N, 11.68.

Treatment of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester with KSCN/Acetone.

A mixture of 0.172 g (0.00177 mol) of potassium thiocyanate and 0.500 g (0.00177 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester was dissolved in 10 mL of ultrapure acetone. The clear yellow solution was stirred at room temperature for 1.5 h, then treated with 10 mL of diethyl ether with no effect. The solution was evaporated under reduced pressure to afford a solid/oil mixture. This was treated with 25 mL of diethyl ether, filtered, dried ($MgSO_4$), and concentrated under reduced pressure to afford 0.50 g of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester: IR (4842) identical to that of the starting material.

Treatment of Dinitrolactone with KSCN/Acetone at Reflux for 1.5 h.

A mixture of 0.40 g (0.0015 mol) of dinitrolactone, 0.9 g (0.0092 mol) of potassium thiocyanate, and 15 mL of acetone was heated at reflux for 1.5 h under a nitrogen atmosphere. The hot, yellow solution was poured into 30 mL of ice/water. The white solid which formed immediately was collected by suction. This was placed in 15 mL of water and heated. The insoluble solid was collected by suction and recrystallized once from acetone/diethyl ether to afford 0.37 g (95%) of dinitrolactone: mp 168-170°; mmp 169-171°; IR (5155) was identical to that of the starting material.

Treatment of 5-Bromo-2-(2-hydroxyethoxy)-benzamide with KSCN/DMSO/110°.

A mixture of 0.50 g (0.0019 mol) of 5-bromo-2-(2-hydroxyethoxy)-benzamide and 1.5 g (0.00154 mol) of potassium thiocyanate was dissolved in 5 mL of dry DMSO. The apparatus was flushed with nitrogen and the solution was heated to 110° for 1.5 h. The clear, hot solution was poured into 25 mL of crushed ice/water with the immediate formation of a white solid. The mixture was warmed to room temperature, the solid was collected by suction and air-dried to afford 0.50 g (100% recovery) of starting material: mp 156-157°; mmp 155-156°.

Treatment of p-Methoxyacetophenone with KSCN/DMSO/110°.

A mixture of 0.75 g (0.005 mol) of p-methoxyacetophenone and 1.5 g (0.0154 mol) of potassium thiocyanate was dissolved in 5 mL of dry DMSO. The apparatus was flushed with nitrogen and the solution heated to 110° for 1.5 h. The clear, hot solution was poured into 25 mL of crushed ice/water with the immediate formation of a white solid. The mixture was warmed to room temperature; the solid was collected by suction and air-dried to afford 0.75 g of starting material: mp 33-34°; mmp 33-35°.

Treatment of 2-Methoxynaphthalene with KSCN/DMSO/110°.

A mixture of 0.75 g (0.0047 mol) of 2-methoxynaphthalene and 1.5 g (0.0154 mol) of potassium thiocyanate was dissolved in 5 mL of dry DMSO. The apparatus was flushed with nitrogen and the solution was heated to 110° for 1.5 h. The clear, hot solution was poured into 25 mL of crushed ice/water with the immediate formation of a white solid. The mixture was warmed to room temperature; the solid was collected by suction and air-dried to afford 0.75 g of starting material: mp 72-73°; mmp 72-73°.

Treatment of 2-Methoxy-3,5-dinitrobenzoic Acid with KSCN/DMSO/110°for 1.5 h.

A mixture of 0.40 g (0.0016 mol) of 2-methoxy-3,5-dinitrobenzoic acid, 1.0 g (0.0103 mol) of potassium thiocyanate, and 5 mL of dry DMSO was heated at 110° for 1.5 h under a nitrogen atmosphere. The hot, yellow solution was poured into 25 mL of ice/water. The yellow solid which formed immediately was collected by suction: IR (4834) 3100 (aromatic C-H stretching), 1700 (carbonyl), 1600 (aromatic C=C stretching), 1560, 1340 (nitro).

The solid was dissolved in tepid water and treated with sulfuric acid. The solid, precipitated from the solution, was collected by suction and recrystallized from water to afford 0.35 g (93%) of 3,5-dinitrosalicylic acid: mp 171-172°; mmp 170-172°; IR (4841) identical to that of material prepared from 2-chloro-3,5-dinitrobenzoic acid.

Treatment of 4-Nitroanisole with KSCN/DMSO/110°for 1.5 h.

A mixture of 0.50 g (0.0033 mol) of 4-nitroanisole, 1.5 g (0.015 mol) of potassium thiocyanate and 5 mL of dry DMSO was heated at 110° for 1.5 h. The hot, clear yellow solution was poured into 25 mL of ice/water with the immediate formation of a solid. It was collected by suction, rinsed several times with water, and air-dried to afford 0.50 g (100% recovery) of 4-nitroanisole: mp 52-54°; mmp 52-54°.

Treatment of 1,2-(Methylenedioxy)-4-nitrobenzene with KSCN/DMSO/110°for 1.5 h.

A mixture of 0.50 g (0.0029 mol) of 1,2-(methylenedioxy)-4-nitrobenzene (Aldrich), 1.5 g (0.015 mol) of potassium thiocyanate, and 5 mL of dry DMSO was heated at 110° for 1.5 h under a nitrogen atmosphere. The hot, clear liquid was poured into 25 mL of cold water with the immediate formation of a solid. It was collected by suction, rinsed several times with water, and air-dried to afford 0.42 g (84% recovery) of 1,2-(methylenedioxy)-4-nitrobenzene: mp 143-145°; mmp 142-144°. The filtrate was acidified with concentrated sulfuric acid and extracted with 3 x 30 mL of methylene chloride. The organic extracts were combined and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded no additional material.

Treatment of 2-Nitroanisole with KSCN/DMSO/110° for 1.5 h.

A mixture of 0.50 g (0.0033 mol) of 2-nitroanisole, 1.5 g (0.015 mol) of potassium thiocyanate and 5 mL of dry DMSO was heated at 110° for 1.5 h under a nitrogen atmosphere. The hot, clear orange solution was poured into 25 mL of ice/water with the formation of an oil. The mixture was extracted with 3 x 30 mL of methylene chloride; the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford 0.45 g

(90% recovery) of 2-nitroanisole as a clear oil: IR (4997) identical to that of the starting material IR (4999) and to Sadtler spectrum # 5864.

Treatment of 2,4-Dinitroanisole with KSCN/DMSO/110° for 1.5 h.

A mixture of 0.50 g (0.0025 mol) of 2,4-dinitroanisole, 1.5 g (0.015 mol) of potassium thiocyanate, and 5 mL of dry DMSO was heated at 110° under a nitrogen atmosphere. The hot, clear orange solution was poured into 24 mL of ice/water. Acidification of the clear yellow solution with 2 mL of concentrated hydrochloric acid caused precipitation of a solid, which was collected by suction, rinsed with water, and air-dried to afford 0.45 g (98%) of 2,4-dinitrophenol: mp 109-111°; mmp 110-111°; IR (5001) identical to Sadtler spectrum # 253.

Treatment of 2-(2-Hydroxyethoxy)-3,5-dinitrobenzoic Acid, Methyl Ester with KSCN/DMSO/110°.

A solution of 0.60 g (0.0020 mol) of 2-(2-hydroxyethoxy)-3,5-dinitrobenzoic acid, methyl ester and 1.5 g (0.015 mol) of potassium thiocyanate was placed in 5 mL of dry DMSO and heated at 110° for 1 h under a nitrogen atmosphere. The hot, clear orange solution was poured into 25 mL of ice/water with the formation of a yellow

solid. The mixture was refrigerated until all of the ice had melted. The yellow solid was collected by suction and air-dried to afford 0.60 g of potassium thiocyanate and impurities: IR (4761).

The filtrate was acidified with concentrated sulfuric acid and chilled in an ice bath. The resulting solid was collected by suction and recrystallized from ethanol to afford 0.50 g of 3,5-dinitrosalicylic acid, methyl ester: mp 125-126° (lit.[156] mp 124-128°); mmp 124-126°; IR (4760), ^{1}H NMR (9769) (acetone), and MS (525) were identical to those of the material prepared from 3,5-dinitrosalicylic acid.

Treatment of 2-Chloro-3,5-dinitrobenzoic Acid with KSCN/Ethanol.

Two grams (0.020 mol) of potassium thiocyanate was dissolved in 10 mL of water. Two grams (0.0081 mol) of 2-chloro-3,5-dinitrobenzoic acid was dissolved in 10 mL 95% ethanol. The two solutions were heated to boiling and then combined. The hot solution was cooled to room temperature and left for 8 h, during which time a yellow solid formed. It was collected by suction, rinsed with water, and recrystallized from ethanol to afford 1.35 g of an unidentifiable substance: mp 199-200°; IR (4106) 3100 (aromatic C-H stretching), 1700 (carbonyl), 1540, 1350 (nitro).

A 0.75-g sample of the material was treated with 25 mL of 10% aqueous hydrochloric acid and heated at reflux for 1.5 h. After the solution was cooled, 0.70 g of an unidentifiable yellow solid was collected by suction; 195-196°; IR (4112) 3100 (aromatic C-H stretching), 1680 (carbonyl), 1600 (aromatic C=C stretching), 1550, 1340 (nitro). No further experimentation was pursued.

Behavior of 2-Chloro-3,5-dinitrobenzoic Acid in KSCN/DMSO.

A 15-mL round-bottomed flask was charged with 1.0 g (0.0040 mol) of 2-chloro-3,5-dinitrobenzoic acid, 2.0 g (0.02mol) of potassium thiocyanate, 5 mL of dry DMSO, and flushed with nitrogen. The temperature of the reaction mixture rose to 35° and a gas evolved. The clear orange solution was stirred for 2 h at room temperature and then poured into an aqueous acid/ice mixture, with formation of an oily suspension. Extractions with methylene chloride, ethyl acetate, and diethyl ether afforded no material.

Other experiments were conducted whereby tetrahydrofuran and tetracyclone were used as possible trapping agents. In both cases, intractable tars were obtained. Heating the reaction mixture of potassium thiocyanate, DMSO, and 2-chloro-3,5-dinitrobenzoic acid caused the reaction mixture to darken within minutes. An intractable material was obtained after the reaction mixture was poured into cold water.

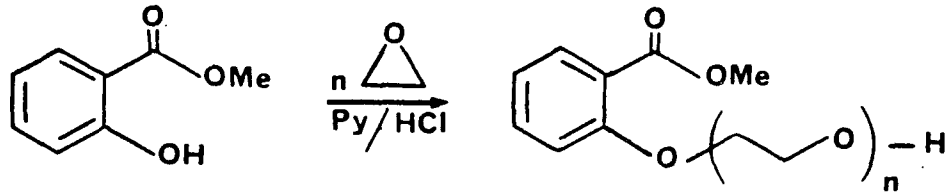
DISCUSSION OF RESULTS

The continued interest in the synthesis of macrolides has resulted in significant advances in the methodologies incorporated into synthetic strategies. Although a large majority of macrocyclic compounds do not contain an aromatic nucleus, ortho-fused macrocyclic lactones do exist and continue to draw attention. The pharmacological properties of compounds such as zearalenone, radicicol, lasiodiplodin, the cis- and trans-resorcylides, and hypothemycin help to sustain an interest in these compounds.[17, 28, 29]

As outlined previously, the goal was to prepare novel ethereal lactones from polyoxygenated ethers derived from methyl salicylate (25). The effect of heteroatoms and large bulky substituents on the aromatic nucleus was envisioned to facilitate ring closure. This exploratory chemistry might then lead to molecules that would exhibit ring-chain tautomerism.[19]

Mobay Chemical Corporation has prepared, for this research group, a large quantity of two polyether esters derived from methyl salicylate (25). The reaction scheme employed by Mobay is depicted below. By this process, the 2-(2-hydroxyethoxy)-benzoic acid, methyl ester (26) and the 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid,

methyl ester (27) were prepared in 5-gal quantities in the form of crude material.



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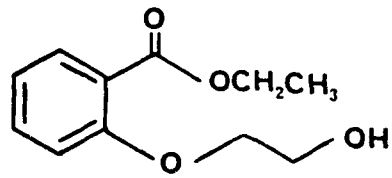
26 n = 1

27 n = 4

Independent studies outside of this laboratory have shown that the 2-(2-hydroxyethoxy)-benzoic acid, ethyl ester (28) exhibits bacteriocidal activity. In the same



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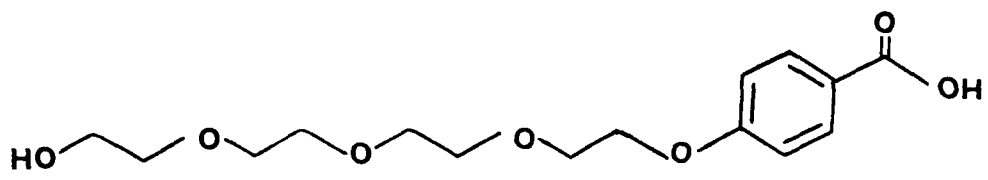
study, the preparation of di-, tri-, and tetra-oxyethylene derivatives of salicylic acid exhibited antimicrobial activity. The activity of such compounds increased as the oxyethylene chain length was increased with the p-tetraoxyethylene derivative 29 showing the highest activity.[104]



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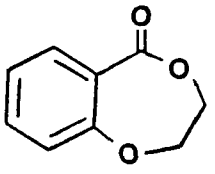
It was felt that a thorough study involving the ester 26 should be conducted. This would include functionalization of the carbonyl group, placement of substituents on the aromatic nucleus, and examination of ring closure reactions on the resulting compounds. In this way, a basis would be established and conclusions drawn so that similar reaction conditions could be applied to the ester 27.

The thrust of this project was to prepare the monolactone 30 and the tetralactone 31. These two compounds would be used as reference compounds to compare the effects of substituents on the aromatic ring and the effect of oxygen atoms in the ethereal lactone upon ring closure.



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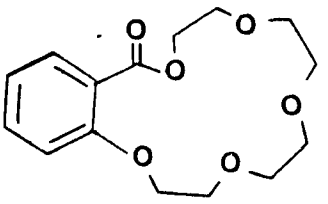


31

The unsubstituted 7-membered ring analog will be referred to as the "monolactone" throughout this dissertation. Its official Chemical Abstract name is 2,3-dihydrox-5H-1,4-benzodioxepin-5-one.

The inclusion of the oxygen heteroatom(s) in the lactone rings provides an advantage, inasmuch as Sicher

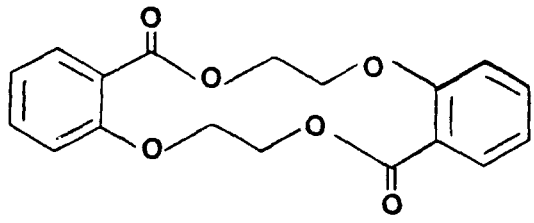
has reported that the replacement of one or more methylene groups of a carbon chain by a heteroatom facilitates cyclization.[18]

The placement of large bulky substituents, such as bromine, chlorine, or nitro groups, on the aromatic nucleus was expected to facilitate ring closure. While ring closure to lactone was the goal, the possibility of ring-chain tautomerism was envisioned.[19, 20] This was especially attractive with substrates that would have bulky substituents on the aromatic nucleus.[19, 20, 105, 106]

The first objective at hand was to purify the ester 26, a crude, dark viscous oil. Klein, in a patent assigned to Texaco Corporation, described the preparation of the ester 26 as well as the monolactone 30.[107] According to the patent information, the ester 26, when heated at distillation temperature, spontaneously lactonizes to afford the monolactone 30. Several other patent reports have appeared in the literature for the preparation of similar β-hydroxyethoxy benzoates.[108-110]

To avoid this impending problem with elevated temperatures, another method of purification was sought. Flash chromatography was chosen as a reasonable alternative.[111] After it was found that diethyl ether was a suitable eluent, it was experimentally determined that a 3-g batch of the crude ester could be partially purified; and that the ester was recovered in 30% yield. It was

found to contain trace amounts of impurities based on the failure to obtain acceptable elemental analyses. Although this method of purification was moderately successful, the process was tedious; and sufficient quantities of purified material were not easily obtained. By this method of purification, no monolactone 30 was isolated. The most surprising result was not in the purification of the ester 26 but the isolation of the dilactone 32 in 7% recovery. TLC analysis, diethyl ether as the eluent, showed that the dilactone 32 was present in the crude mixture of the ester 26.



32

A trial purification of the ester 26 by kugelrohr distillation was investigated, in spite of the literature precedent for lactonization. Distillation of the crude ester 26 was complicated by vigorous frothing and foaming of the material when the reaction vessel was evacuated. This problem could be minimized in the following manner. The ester 26 was first dissolved in methylene chloride and then washed successively with aqueous acid and aqueous base. The solvent was removed under reduced pressure without foaming and frothing occurring. Distillation of

the residue was then possible and no lactonization was observed, the ester being recovered in 50% yield.

Another approach to the problem of foaming was to dissolve the crude ester 26 in methylene chloride and then remove the solvent under reduced pressure but without the acid and base washing. While the vessel was still warm, the liquid ester could be placed under a vacuum with only a minimal amount of foaming. By this method, during the distillation process, lactonization to 30 did occur as evidenced by ^{1}H NMR. Therefore, there must be an agent, possibly acid remaining from the original preparation of the ester 26 that aids in lactonization, which is removed by first washing the ester 26 as described. This latter method of purification was used for preliminary synthetic preparations attempted in this laboratory; the monolactone 30 was not removed in most instances prior to use. In this way, a crude 20-g sample of ester 26 would afford, after distillation, approximately 8 g of ester/monolactone as a clear, yellow oil.

A large-scale distillation was performed on a vacuum line system. Several hundred grams of purified ester/monolactone were collected in a few hours in a batch process. ^{1}H NMR analysis showed the presence of the monolactone 30, along with the ester 26. This method of purification proved to be the most useful, and most synthetic work was performed with this material.

The combined residues from the vacuum distillations were combined and found to contain substantial amounts of the dilactone 32. It could be separated from the tarry byproducts by washing the mixture with carbon tetrachloride and then separating the solid dilactone 32 from the solvent by suction. This solid was then recrystallized from acetone/water to afford the dilactone.

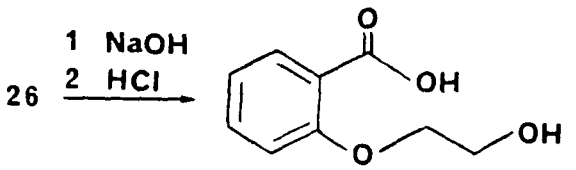
The best method of purification of the ester 26, in terms of time, purity of samples, and recovery, was that performed on a Waters' Associates HPLC. In a private communication from Dr. Joan Newburger, a suitable method to purify the ester 26 and dilactone 32 was described where a mixture of 40% ethyl acetate/60% hexane was used as the solvent.[112] A typical HPLC run with a 20-g sample of the crude ester 26 would afford 6.0 g (30% recovery) of analytically pure ester 26 and 1.0 g (5%) of analytically pure dilactone 32. Similar HPLC purification of the vacuum distilled ester/monolactone afforded, in addition to 26 and 32, the monolactone 30.

It should be noted that neither in the flash chromatography purification nor in the HPLC purification of the crude ester 26 was there any amount of monolactone 30 isolated. This confirms that the lactonization occurs when the crude ester 26 is distilled without first being washed with aqueous acid and base solutions.

Once ester 26 in reasonably pure form was available, a series of experiments to explore its chemistry was

undertaken. Functionalization of the ester carbonyl was planned so that lactonization studies could be performed. A large scale preparation/purification of a solid derivative from the ester/monolactone mixture was desired so that pure compounds would be on hand for subsequent experimentation.

Base hydrolysis of the ester 26 under various conditions afforded the carboxylic acid 33 in 35-95% yields. This variation in recovery might be attributed to the competing solubility of 33 in water because of the hydrophilic nature of the polyfunctional carboxylic acid. The partitioning of the carboxylic acid 33 in most organic



33

solvents was very poor. Only approximately 30% of the expected acid was recovered when diethyl ether or chloroform was used as extraction solvent. Methylene chloride was found to be the most suitable extraction solvent even though the partioning was erratic. On several occasions, upon acidification of the basic solution which contained the carboxylate salt, an unidentified white solid was obtained. Spectral analysis of this material as well as elemental analysis

showed that the substance contained only a small percentage of organic material. This solid did not melt below 300° and would sinter when placed in a flame, leaving a white residue.

Purification of the carboxylic acid 33 by kugelrohr distillation was impeded by lactonization to the corresponding monolactone 30. (An identical observation was made by Rousselle and coworkers.[113]) Treatment of 33 with $MgSO_4$ and $NaHCO_3$ during heating to distillation temperature did not alleviate this problem. The carboxylic acid 33 was used without further purification in subsequent reactions.

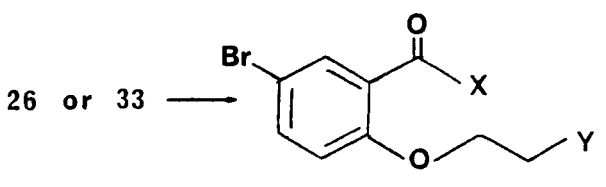
To effect lactonization of the carboxylic acid 33 to the monolactone 30, the procedure of Brewster and Ciotti was found to be very effective.[114] Treatment of a solution of the carboxylic acid 33 in cold pyridine with p-toluenesulfonyl chloride gave the monolactone 30 in quantitative yield. After purification of the product by kugelrohr distillation, the monolactone 30 was isolated as the sole product, either as a liquid or as a clear, crystalline solid with a melting point of 35-36°. The monolactone 30 exhibited a unique ^1H NMR spectrum for the methylene protons. The methylene protons appear as a singlet at 4.55 ppm even though they are not chemically equivalent. High field ^1H NMR at 90 MHz did not resolve this singlet.[113]

Another preparation of the monolactone 30 was accomplished by dehydration of the ester 26 with aluminum oxide.[115-117] This method has been used by Posner, Matta, and coworkers as a highly effective way to acetylate primary alcohols in the presence of secondary alcohols. Lactonization of the ester 26 to the monolactone 30 was done at room temperature with no apparent formation of the dilactone 32.

As a means to help effect ring closure, the introduction of substituents in the aromatic nucleus was desired. With this strategy in mind, bromination and nitration were chosen as a suitable means of incorporating such groups. Bromination of the ester 26 with glacial acetic acid and two equivalents of bromine afforded the 5-bromoester 34 in good yields. Attempts to dibrominate the ester 26 by using a large excess of bromine, bromine and iron filings, or by heating the bromine/glacial acetic acid mixture were unsuccessful. However, when the ester 26 was heated with excess bromine in glacial acetic acid, the acetylated product, 5-bromo-2-(2-acetoxyethoxy)-benzoic acid, methyl ester 35 was obtained.

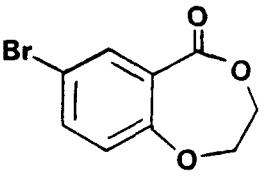
Treatment of the carboxylic acid 33 with glacial acetic acid and excess bromine for one day at room temperature resulted in the formation of 5-bromo-2-(2-acetoxyethoxy)-benzoic acid 36.

Aqueous acid hydrolysis of the 5-bromoester 34 afforded the corresponding 5-bromoacid 37 in quantitative yields. An attempted dehydration of 37 with $POCl_3$ met with failure. TLC analysis indicated that no lactonization had occurred. This method was not investigated any further.



34 X = OMe Y = OH
35 X = OMe Y = OAc
36 X = OH Y = OAc
37 X = OH Y = OH

Lactonization of the 5-bromoacid 37 to the 5-bromolactone 38 was accomplished however by the procedure

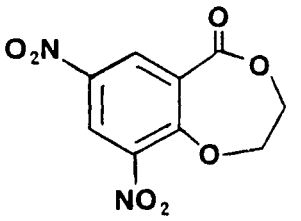


38

of Brewster and Ciotti.[114] To confirm the structure of the lactonization product a sample of the monolactone 30 was brominated with excess bromine in acetic acid. Six equivalents of bromine were required before bromination of the lactone 30 would take place. The product isolated

from this reaction was identical to the 5-bromolactone 38 prepared from the 5-bromoacid 37.

Nitration of the ester 26 was effected when a cold solution of concentrated sulfuric and nitric acid was used. In these cases, only the dinitrolactone 39 was isolated. A possible explanation for the ease of lactonization centers on the nitro group adjacent to the hydroxyethoxy side arm. The steric bulk of this group may



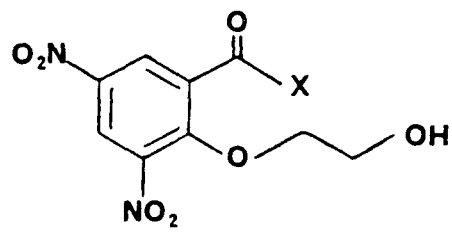
39

force the hydroxyl portion into closer proximity to the ester, thereby helping to facilitate ring closure. ^1H NMR studies demonstrated that when the ester 26 was treated with concentrated sulfuric acid, no appreciable amount of monolactone 30 was formed. This lends support that the nitro group adjacent to the hydroxy side arm has an important effect on the cyclization. The effect will be discussed in more detail in a later section of this dissertation.

There is no apparent explanation for why dinitration occurs, however. Attempts to mononitrate the monolactone 30 were unsuccessful when glacial acetic acid/nitric acid

was used as the nitrating medium. Further work in this area is warranted.

Transesterification of the dinitrolactone 39 with methanol and a few drops of concentrated hydrochloric acid afforded the dinitro methyl ester 40 as a thick yellow oil. If a trace of acid remained after workup, or if concentrated sulfuric acid was used, this was enough to catalyze relactonization to the dinitrolactone 39. Great



40 X = OMe

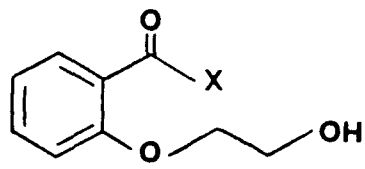
41 X = OH

care had to be exercized to ensure that all of the acid had been neutralized before the final removal of the extraction solvent.

Acid hydrolysis of the dinitrolactone 39 to generate the dinitroacid 41 was accomplished with aqueous 20% hydrochloric acid. If the acid concentration was below 20%, the dinitrolactone 39 was recovered as the sole product. Base hydrolysis of the dinitrolactone 39 gave various results dependent upon the reaction conditions. These results will be discussed in the following chapter.

Ammonolysis of the ester 26 proved to be an efficient method to derivatize the liquid ester into a solid

benzamide. Conversion of the ester 26 to the amide 42 was carried out by treating the ester with an excess of aqueous 30% ammonium hydroxide at room temperature for a period of 1 h. After removal of the aqueous solution, the re-



42 X = NH_2
43 X = $NHCH_3$
44 X = $N(CH_3)_2$

sulting solid mass was recrystallized to afford the amide 42 in good yields.

The N-methyl amide 43 and the N,N-dimethylamide 44 were prepared in the same manner as outlined above for the unsubstituted amide 42. The N-methylamide 43 was easily recrystallized and characterized by the usual methods, whereas the N,N-dimethylamide 44 remained an oil and was always contaminated with some amount of impurities. Attempts at purification of this oil resulted in an intractable tar. No further work on this compound was carried out.

It is interesting to note that in the N-methylamide 43 there are 2 carbonyls and 2 N-methyls observed in the ^{13}C NMR spectrum, whereas only one carbonyl and one N-methyl are reported for N-methyl benzamide.[118] The ^{1}H NMR of 43 shows the amide NH as a broad singlet at 8.6-7.9 ppm and two methyl singlets at 2.9 and 2.7 ppm. A single methyl peak in the ^{1}H NMR spectrum of N-methyl benzamide[119] can be attributed to the predominance of the sterically

favored Z conformer. Because of the ortho substituent, it would be expected that the barrier to rotation about the C-N bond in 43 would be even higher than that in N-methyl benzamide.[120] It is likely that compound 43 adopts one of two Z conformations such that the N-methyl does not encounter 1,6 interactions with either an aromatic ring proton or the 2-(2-hydroxyethoxy) functionality. The doubling of the methyls and carbonyls could be explained by significant population of the two Z conformations of the amide 43 as depicted in Figure 11. The amide is ideally constituted for intramolecular hydrogen bonding, which may be an important factor in stablization of one conformer.

Conformations of 2-(2-Hydroxyethoxy)-N-methylbenzamide

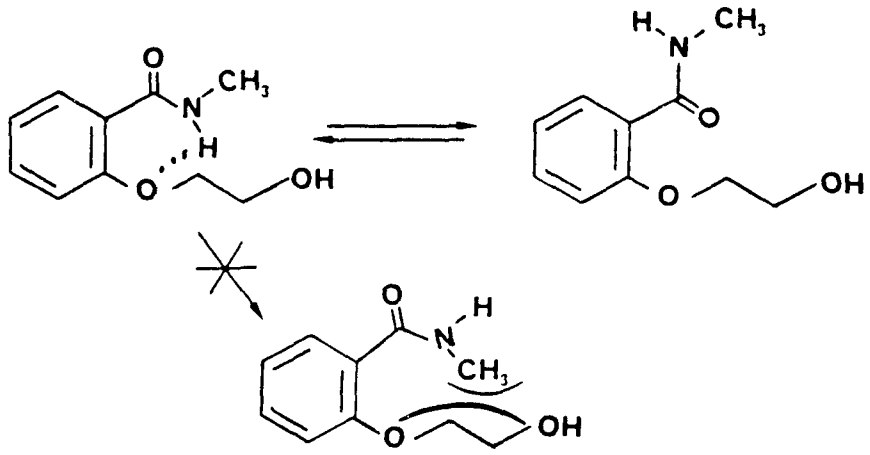


Fig. 11

This hydrogen bonding phenomenon is probably occurring in the amide 42 but is not observed because the hydrogens on the amide moiety are isochronous. This is not the case in 43 where the amide hydrogen is anisochronous. Amide 44 cannot exhibit this phenomenon because of the lack of hydrogens on the amide nitrogen.

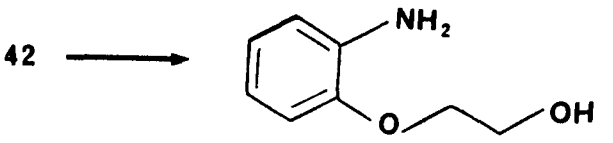
A possible ^{1}H NMR and ^{13}C NMR study could be done with dynamic NMR to determine the coalescence temperature of the amide 43. From this data, the energy of rotation about the amide carbonyl could be calculated. IR data does not exhibit any unusual characteristics in 43 except for a broad amide carbonyl centered at 1640 cm^{-1}. The amide NH is overlapped by the alcohol OH and therefore definitive assignments or conclusions that hydrogen bonding is actually occurring cannot be made from this information.

Various conditions for the hydrolysis of the benzamide 42 were explored. Treatment with aqueous base followed by acidification resulted in the formation of the carboxylic acid 33 in 10-80% yields. These inconsistent yields are again attributed to the unfavorable partitioning of the carboxylic acid 33 in the extraction solvent. Preparation of the carboxylic acid 33 by aqueous acid hydrolysis of the amide 42 proved to be a more effective method with generally greater than 70% yields of the carboxylic acid 33 isolated. The carboxylic acid 33 prepared from the aqueous acid hydrolysis of the amide 42 was used in subsequent reactions without any further purification.

One reason for the increase in isolated yields of the carboxylic acid 33 when aqueous acid was used to hydrolyze the amide 42 may lie in the workup. Base hydrolysis of the ester 26 or the amide 42 was generally done with

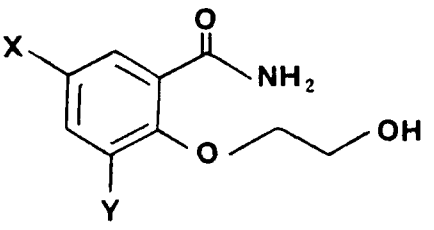
relatively large volumes of aqueous solution, approximately 100 mL. However, in the aqueous acid hydrolysis, a minimal amount of water was used, generally 25 mL or less. In the latter case the partioning of the acid 33 into the organic layer seems to be enhanced.

With a method established for the preparation of the amide 42, a series of experiments was attempted to effect a Hofmann Rearrangement of the amide to the corresponding



45

aromatic amine 45.[121] The amide 42 when treated with bromine in 5% aqueous sodium hydroxide at ice-bath temperatures produced the 5-bromoamide 46. The yields in this reaction were quantitative and reproducible. The 5-bromoamide 46 was subjected to acid hydrolysis with refluxing 20% aqueous hydrochloric acid for 6 h, which



46 X = Br Y = H

47 X = Y = NO_2

resulted in the quantitative formation of the 5-bromoacid 37.

A survey of the literature revealed that the amide 42 and the 5-bromoamide 46 had previously been prepared by Way and Faust. The general reaction scheme is outlined below (Fig. 12). These two compounds were found to exhibit hypnotic properties as well as being central nervous system depressants.[122, 123]

Preparation of ortho Substituted Salicylamides

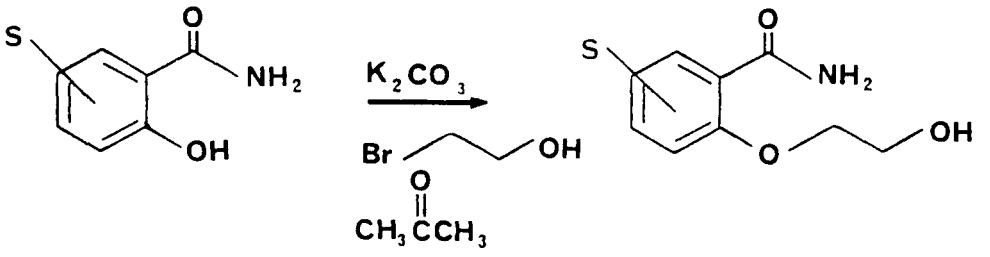


Fig. 12

Nitration of the amide 42 to the corresponding dinitroamide 47 was effected when similar conditions to those for the nitration of the ester 26 were used. When the reaction temperature was maintained below 10°, the product isolated was the dinitroamide 47. If the reaction temperature was not monitored carefully and the temperature of the reaction mixture was allowed to rise above 25°, some amount of the dinitrolactone 39 was observed by TLC analysis.

With the three amides 42, 46, and 47 available, diazotization experiments were conducted to observe whether ring closure would occur and, if so, what effect the substituents had upon the reaction.[124] When the unsubstituted amide 42 and the 5-bromoamide 46 were treated under diazotization conditions, the products isolated were the corresponding carboxylic acids, 33, and 37. However, diazotization of the dinitroamide 47 afforded the dinitrolactone 39 in quantitative yield. Aqueous acid hydrolysis of the dinitroamide 47 also afforded the dinitrolactone 39 in quantitative yields. These observations lend support to the conclusion that the nitro group adjacent to the 2-(2-hydroxyethoxy) portion of the molecule exerts a favorable effect on the ease of lactonization.

To this point, none of the compounds synthesized exhibited ring-chain tautomerism as judged by IR, ^{1}H NMR or ^{13}C NMR (Fig. 13). It was proposed that in order to observe ring-chain tautomerism, compounds with a more electrophilic site other than a carboxylic acid, ester, or amide attached to the aromatic nucleus might tautomerize.[105] The presence of bulky substituents on the aromatic nucleus might also accentuate the tendency for ring tautomer formation.[19]

Dehydration of the amide moiety to the nitrile would allow a testing of the first factor. If ring-chain tautomerism occurred, an imine type ring tautomer would be

observed by IR, ^{1}H NMR, or ^{13}C NMR. Spectroscopic measurements could then provide information of the ratio of ring versus chain tautomer composition that may exist in various solvent systems.

A nitrile was deemed a suitable choice for the nucleophilic attack of the hydroxyl group of the 2-(2-hydroxyethoxy) functionality. This strategy was chosen because of the ease of preparation of the amides 42, 46, and 47 in large quantities. There was also ample precedent for the attack of an alcohol at a nitrile center such that ring-chain tautomerism was observed.[125] Several dehydration procedures were examined where the unsubstituted amide 42 was used for model studies.

Ring-chain Tautomerism (General Scheme)

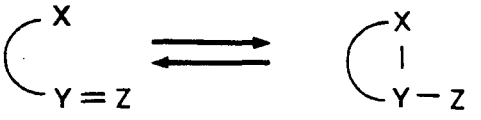
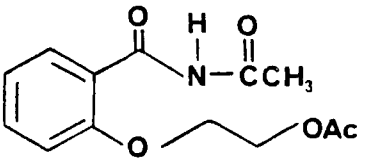


Fig. 13

The first procedure chosen for nitrile formation was with acetic anhydride.[126] When the amide 42 was treated with acetic anhydride at reflux temperature for 3.5 h, a mixture of products was obtained as a thick oil after the

removal of excess anhydride. Purification of the material by kugelrohr distillation afforded a mixture of two



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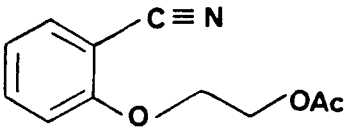
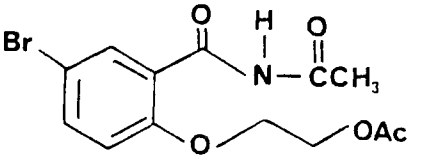


49

compounds 48 and 49. TLC and ^{1}H NMR evidence indicated that the major component of the mixture was 49. When the amide 42 was subjected to identical reaction conditions for 24 h, an increase in the amount of 48 was noted. IR, MS, and ^{1}H NMR spectral evidence supported the structure of these two compounds. In the IR spectrum, the broad OH and NH_2 stretch of the amide 42 was replaced with a sharp NH stretch at 3320 cm^{-1}. Other prominent spectral features in the IR included the presence of a nitrile stretch at 2210 cm^{-1} and three carbonyls at 1750, 1720, and 1700 cm^{-1} for the acetates as well as a broad stretch between 1300-1220 cm^{-1} typical of acetates. Imides typically have two carbonyl stretches between 1770-1680 cm^{-1}. The carbonyls at 1750 and 1700 cm^{-1} were assigned to the imide carbonyls. The remaining carbonyl was assigned to the acetates of 48 and 49, the two being indistinguishable.[127] ^{1}H NMR spectra were useful in

determining the presence of 48 formed in the reaction mixture. In addition to the acetate methyl resonance at 2.0 ppm, another peak appeared at 2.55 ppm which was assigned to the imide acetyl methyl. The mass spectrum of the liquid showed molecular ions for both 48 and 49. Purification of the liquid by simple distillation was unsuccessful; both liquids distilled at the same temperature. No further experimentation was performed on compounds 48 or 49.

When the 5-bromoamide 46 was treated with acetic anhydride at reflux temperature, it was possible to isolate a single product. The material produced from this reaction, a solid and easily purified, proved to be N-acetyl-5-bromoamide 50. The structural assignment was



50

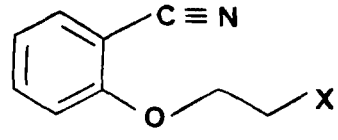
confirmed with IR, MS, ^{1}H NMR, elemental analysis and ^{13}C NMR spectroscopy. As in the unsubstituted amide 42, the broad OH and NH_2 stretch of the parent amide 46 was replaced with a sharp NH stretch at 3360 cm^{-1}. There were two carbonyls at 1760 and 1700 cm^{-1} with no nitrile stretch observed. The carbonyl at 1760 cm^{-1} was very

broad; possibly the acetate carbonyl and the higher energy imide carbonyl overlap and are not resolved. The ^{1}H NMR spectrum confirmed that there were two acetyls within the molecule which exhibited chemical shifts at 2.5 and 2.0 ppm.

As a milder means of dehydration of the amide to a nitrile, the method of Casini was chosen.[128] Treatment of the amide 42 with trifluoroacetic anhydride/pyridine at ice-bath temperature afforded a mixture of products as a thick yellow oil. Preliminary IR results and TLC analysis showed it to be a mixture of products. The IR spectrum showed the presence of a carboxylic acid OH stretch, a nitrile stretch at 2220 cm^{-1}, several carbonyls, and an acetate stretch between 1200-1100 cm^{-1}. Hydrolysis of the material with an aqueous solution of sodium hydroxide and methanol afforded a clear oil after extraction and removal of the methanol. The IR spectrum showed a broad alcohol stretch between 3600-3100 cm^{-1}, a nitrile stretch at 2220 cm^{-1}, and a stretch at 1660 cm^{-1}. This is the first time a carbonyl was noted at this low an energy. This stretch could be assigned to an amide carbonyl or an imine C=N stretch. The disappearance of the acetate functionality was noted by the loss of the carbonyl absorptions as well as the disappearance of the strong absorption between 1220-1100 cm^{-1}. This might possibly be the first ring-chain tautomer observed from this study. No further work

was pursued on this material because of insufficient quantity.

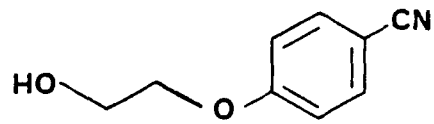
The method of preparation for nitrile formation developed by Morita and coworkers *via* dichlorocarbene was attempted in modified form.[129] Of the various conditions that were tried, the most favorable was to warm the amide 42 in chloroform to 56°, at which point it dissolved. Then, after the introduction of the phase-transfer catalyst, two equivalents of aqueous sodium hydroxide were added to the solution over a period of 3 h.



51 X = OH
52 X = Cl
53 X = OCHO
54 X = I

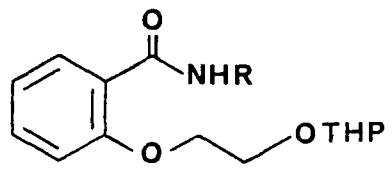
It was determined by TLC analysis, IR, ^{1}H NMR, and MS that the crude reaction mixture consisted of 51, 52, and 53. This reaction mixture was not unexpected because of the competition between the dehydration of the amide and the chlorination of the alcohol. These structural assignments were based on the following experimental observations. The ^{1}H NMR spectrum of the crude material showed a formyl proton at 8.2 ppm. IR information included an alcohol stretch, nitrile, and an aldehyde

literature, 4-(2-hydroxyethoxy)-benzonitrile, (55) has been described as showing fungicidal activity.[130-132]



55

To prevent side reactions, such as the ones observed in the nitrile formation under phase-transfer conditions, protection of the alcohol functionality within the amide 42 was attempted by forming the THP derivative of the alcohol. What was found was that the DHP protected not only the alcohol but the amide as well. When the reaction was carried out with various amounts of DHP and tosic acid and monitored by TLC, it was noted that two products formed simultaneously, under all conditions. The compounds were most likely 56 and 57. Workup of the reaction mixtures afforded clear oils which were examined by IR and ^1H NMR spectroscopy. These spectra both showed a large amount of aliphatic functionality which was due to the THP protecting group. The IR showed that the alcohol was protected; the broad OH stretch had been replaced with a set of sharp NH_2 stretches due to the mixture of the two amides 56 and 57. Two carbonyls were present at 1710 and



56 R = H

57 R = THP

1660 cm^{-1}. The carbonyl at the higher frequency was probably due to the N-THP amide and the other would then correspond to the unprotected amide carbonyl.

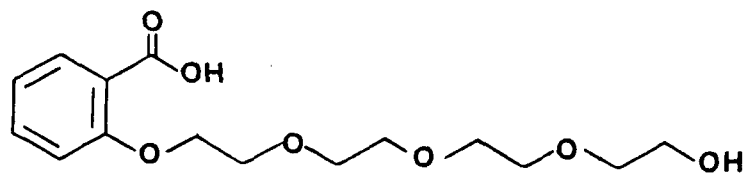
Because the method to cleave an N-(2-tetrahydropyranyl)-amide requires phosphoric acid, which would also cleave the THP-protected alcohol, this method of protection was not pursued any further.[133-135]

Attention was directed to chemical transformations of the ester 27. The knowledge acquired from the synthesis of previous compounds was to be applied to 27. It was found that the ester 27 could be partially purified by kugelrohr distillation. The IR and ^1H NMR characteristics of the distillate are consistent with the structure. In the IR the aliphatic region was much more pronounced than in the ester 26. The alcohol OH was broad and the ester carbonyl was present at 1730 cm^{-1}. The methylene, methyl, and hydroxyl portions of the ^1H NMR were observed to be a series of overlapping multiplets which integrated for the correct number of protons required for the structure 27.

Material obtained by HPLC purification was identical to the distilled ester by IR and ^{1}H NMR analysis. Although TLC indicated there were other substances in the crude ester 27, none was isolated by these methods.

Base hydrolysis of the ester 27 afforded the corresponding carboxylic acid 58 after acidification and repeated extractions of the aqueous phase. Suitable IR and ^{1}H NMR spectra were obtained without purification of this material. Examination of the IR spectrum showed that there was a broad carboxylic acid and hydroxyl stretch between 3600-2500 cm^{-1} and a carbonyl at 1730 cm^{-1}. The carboxylic acid and the hydroxyl protons were located within the aromatic multiplet, centered between 8.1-6.9 ppm. The aliphatic methylene protons were observed between 4.3-3.2 ppm as a series of overlapping multiplets.

Lactonization of 58, by the procedure of Brewster and Ciotti was attempted, but purification of the product by

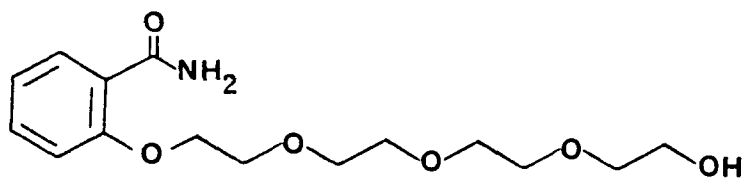


58

kugelrohr distillation resulted in an intractable tar that could not be identified.

A trial nitration of the crude ester 27, where reaction conditions were identical to the nitration of the ester 26, afforded the dinitrolactone 39 in a substantial amount. Careful examination of TLC information, however, showed ester 28 was a minor component in the kugelrohr distilled ester 27. IR and ^{1}H NMR data also support the conclusion that very little ester 26 was present in the distilled material. To account for a crude yield of the dinitrolactone 39 in greater than 50%, it would appear that the polyether chain is cleaved under acidic conditions used in the nitration. Investigation of this possibility was not pursued and should be examined in more detail.

Ammonolysis of the ester 27 with aqueous 30% ammonium hydroxide afforded a clear yellow oil after workup. The oil was identified as the amide 59 by IR and ^{1}H NMR. IR



59

data showed a broad NH_2 and OH stretch between 3600-3100 cm^{-1}. The ester carbonyl at 1730 cm^{-1} was replaced by a new amide carbonyl at 1660 cm^{-1}. Purification of the material by distillation and by passage through a small

column of silica gel did not afford a pure product. Further work on this material was not pursued.

The ^{1}H NMR spectra of the acids, esters, lactone, amides, and dilactone with no aromatic sustituents all displayed a characteristic pattern in the aromatic region. The aromatic proton ortho to the carboxy group is farthest downfield relative to the remaining protons. A similar trend has been noted by Malmberg and Wehrmeister in separate studies.[28, 136] They report that the magnitude of the downfield position is dependent upon the nature of the carbonyl function. They found that the downfield position follows the order: acid > ester > lactone. In Table I are compiled the observed data for the unsubstituted amides, acids, esters, and lactone. In all but one case, the NMR solvent was $CDCl_3$. It is therefore possible to state with reasonable confidence that the downfield shift of the aromatic proton ortho to the carbonyl functionality follows the order: amide > acid > ester > lactone. This information serves as a general guide in assigning the proton ortho to the carbonyl function.

In the present study, several amides were available to be included for the first time. In Table I, it is evident that the chemical shift of the aromatic proton ortho to the amide carbonyl is shifted farthest downfield in comparison to the acid, ester, or lactone values. This may be due to an attraction between the aromatic proton

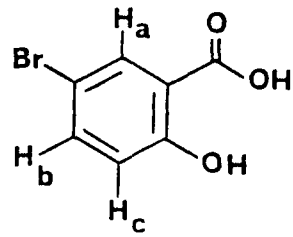
and the resonance stabilized carbonyl functionality. This effect would decrease as the carbonyl becomes less polarized from an amide or an acid to an ester. This effect would diminish as steric or geometric constraints are placed upon the molecule. One would predict that an amide or acid would have the greatest effect on the ortho proton followed by an ester and then the lactone. This trend is followed; the lactone which is constrained shows the least effect on the magnitude of the chemical shift of the ortho proton.

An examination of ^{1}H NMR spectra for the brominated compounds does not reveal the predicted pattern as seen in Table II. When only the downfield chemical shift of the proton ortho to the carbonyl functionality is considered, the apparent order is amide > lactone > acid > ester. If the difference between this ortho proton and the remaining protons is calculatd, then the order is changed to lactone > amide > acid > ester. With the exception of the lactone, the predicted order is followed. There is no apparent reason for this reversal in order.

In order to assign which aromatic proton was actually ortho to the carbonyl function, a degradation of the supposed 5-bromoacid 37 was performed with BBr_3 in methylene chloride.[137, 138] This compound was chosen for two reasons. The 5-bromoacid 37 exhibited a typical aromatic splitting pattern identical to all of the brominated compounds; and the 5-bromoacid 37 could be

related chemically to other brominated compounds by a single transformation.

Degradation of the 5-bromoacid 37 afforded 5-bromosalicylic acid 60. This same compound was previously prepared from salicylic acid. ^1H NMR spectra showed the degradation product from the 5-bromoacid 37 and the 5-



60

bromosalicylic acid 60 were identical. Examination of the coupling constants thus allowed the unequivocal assignment of the three aromatic protons in the brominated compounds.

The coupling constants for H_a, H_b, and H_c were measured. H_a had a small meta coupling constant of 2.5 Hz as expected. H_b was a doublet of doublets with an ortho coupling of 10 Hz and a meta coupling of 3 Hz. H_c, a doublet, had a large ortho coupling constant of 10 Hz; no para coupling with H_a was observed.

Similar correlations cannot be drawn when the dinitrated compounds are considered. In all cases, the two remaining aromatic protons are shifted downfield relative to the parent substrates and are observed to be

doublets of doublets. This splitting pattern serves to confirm the dinitrated structure.

In all of the compounds synthesized, the aliphatic methylenes exhibited complex splitting patterns. Each methylene, according to first order rules, should be a triplet; however, there is fine structure within each of these triplets. Solvents such as acetone, DMSO, or $CDCl_3$ had no effect on this fine structure in the multiplets. The methylenes in all structures are situated between 4.6-3.5 ppm except for those in the dinitrolactone 38, which are observed between 5.0-4.7 ppm. This multiplicity holds in all cases except for the monolactone 30, the 4-bromo acid acetate 36, and the 5-bromolactone 38. In these three compounds, the methylenes are accidently equivalent and appear as singlets at 4.55 ppm even at 90 MHz.

Several inclusive comments may be made about the ^{13}C NMR shifts of compounds synthesized in this study. The aromatic carbon bearing the 2-(2-hydroxyethoxy) or lactone unit was shifted farthest downfield relative to the remaining aromatic carbons. This was independent of any added substituent effects. Carbons 1 and 3 (See Fig. 14) were consistently shifted farthest upfield, in agreement with the large negative substituent parameter associated with the 2-(2-hydroxyethoxy) functionality. A small trend established itself where the dinitrolactone 39, 5-bromolactone 38, and the monolactone 30 all had their

Assignment of Aromatic positions for ^{13}C NMR

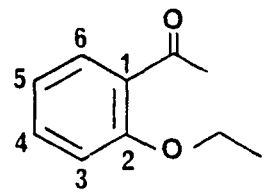


Fig. 14

respective C-2 carbon shifted upfield relative to the corresponding ester. This may be attributed to possible ring strain caused by the 7-membered lactone.

The aliphatic chemical shifts of the molecules, whether cyclic or acyclic, appeared not to be affected by lactonization or substituents of the aromatic nucleus. Generally, the carbon that was adjacent to the phenoxy was farthest downfield, approximately 70 ppm relative to TMS, and the carbon adjacent to the hydroxyl was upfield, approximately 60 ppm. This same trend was noted in 2-phenoxyethanol with chemical shifts of 69 ppm and 61 ppm, respectively. The ^{13}C NMR chemical shifts were compiled and compared with calculated values.[139, 140] Calculation of predicted values required substituent parameters for the 2-(2-hydroxyethoxy) substituent and the 7-membered lactone ring, others being already published. The substituent parameter value of the 2-(2-hydroxyethoxy) unit was deduced from the ^{13}C NMR shifts in 2-

phenoxyethanol by subtraction from benzene values.[141] With all of the necessary substituent values, calculation of the predicted chemical shifts could be performed by using one of the following three methods.

The calculated values for the ^{13}C chemical shifts for all of the amides, esters, lactones, and acids were determined by using the following equation:

$$C^i = A + n_{ij}B_j$$

where C^i is the calculated carbon chemical shift for the i-th carbon atom. The term n_{ij} is the number of substituents in the j-th position (C-1, ortho, meta, para) relative to carbon i and B_j is the substituent parameter for the j-th position.[142]

In Method 1, the value for A is that of benzene, 128.5, relative to TMS. Since there were no substituent effects or values known for a lactone by this method, the calculated values for the acyclic esters and lactones are identical. Levy and Wherli state that when many substituents are placed on a benzene ring, the additivity effects often break down, especially when there are steric interactions between functional groups.[139, 140]

In Method 2, A is the carbon chemical shift of the corresponding substrate; i.e. lactone, acid, amide, or ester (See Table III).[143] The values used are the actual chemical shifts of each compound. The original assignment of the chemical shifts to the ring carbons was based on

calculations with Method 1; that is, the A value for benzene (128.5) was used.[143]

In Method 3, A is the carbon chemical shift value of the corresponding carbon in the 2-methoxybenzoic acid or the methyl ester.[144, 145] (See Table III)

The most noticeable difference in chemical shifts, relative to one another, is in the C-2 and C-3 carbons of the monolactone. The upfield shift in the C-2 carbon may be due to ring strain in the 7-membered lactone. There is no definitive explanation why the C-3 carbon should exhibit a downfield shift when compared to the other substrates. A possibility is that the ether oxygen in the lactone ring might exhibit some type of deshielding effect on the C-3 carbon through the system. Calculated chemical shifts by Methods 1 and 3 are tabulated in Table III for the parent compounds.

In general, the values calculated by Method 1 for the substrates give a better overall fit than by Method 3. The amide could not be analyzed by Method 3. No ^{13}C values were found for 2-methoxybenzamide. The C-3 carbon experiences a large upfield shift due to a large (-13.8 ppm) substituent effect for the 2-(2-hydroxyethoxy) function.

Calculated and actual chemical shifts are shown in Table IV for the mono or disubstituted compounds. From Table IV, it becomes evident that Method 2 provides calculated values with the best fit to the actual values.

This is reasonable since change in the A values should improve the precision between the actual and calculated values. This has been noted in a similar study where salicylic acid derivatives were correlated with different A base values.

In Table IV a few highlights may be noted. First, the calculated C-2 and C-3 values in the dinitro compounds vary the most from the actual chemical shifts. This is probably due to steric crowding as stated by Levy and Wehrli.[139, 140] This is not the case in the brominated or unsubstituted compounds. Second, Method 2 gives a better correlation than the other two methods. However, by any of the three methods, the actual and calculated chemical shifts usually vary by less than 4 ppm.

Low resolution mass spectral analysis of the unsubstituted compounds showed several trends. The amide 42, ester 26, carboxylic acid 33, and dilactone 32 all had molecular ions at their respective molecular weights. All of these compound had a base peak at 120 m/e, with similar fragmentation thereafter. The monolactone 30 also followed the same fragmentation pathway, although the mass spectrum always contained a small amount of material with a higher molecular weight than that of the monolactone 30.

The brominated analogs of the amide, acid, ester, and lactone all showed their respective molecular ions as doublets because of the isotopes of bromine. All of these compounds have as the base peaks 198, 200 m/e and give

identical fragmentations thereafter. A possible fragmentation pathway to account for these observations in the unsubstituted and brominated compounds is outlined in Figure 15.[146, 147]

The dinitro acid 41, dinitro methyl ester 40, and dinitro amide 47 did not give their respective molecular ions. Instead, all of these compounds gave as the highest molecular ion mass peak that of the parent dinitrolactone 39 (m/e of 254). All of these compounds had a base peak at 194 m/e. The subsequent fragmentation pattern again was identical for all of the dinitrated compounds. A possible fragmentation pathway is outlined in Figure 16.[146, 147]

Mass Spectral Fragmentation of Unsubstituted and Brominated Compounds

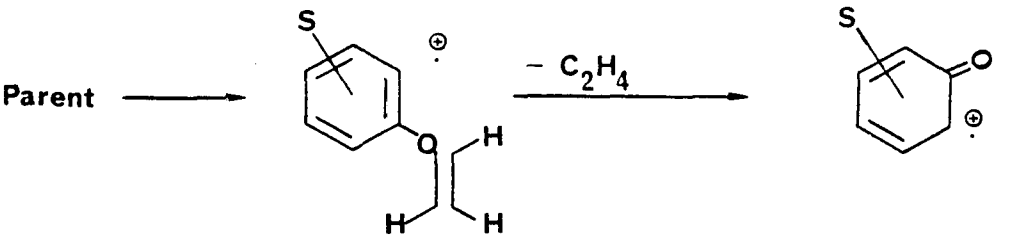


Fig. 15

Infrared spectra of the compounds reported in this section contain, in general, those features expected from

empirical correlations. A few characteristics to be noted are the aromatic C=C stretching frequencies which occur as two strong bands at 1610-1590 cm^{-1}.[148] This is common to all of the compounds reported thus far. The esters 26, 27, 34, and 40 all had carbonyl stretching frequencies between 1720-1730 cm^{-1}, in agreement with known benzoate esters.[149]

Mass Spectral Fragmentation of Nitrated Compounds

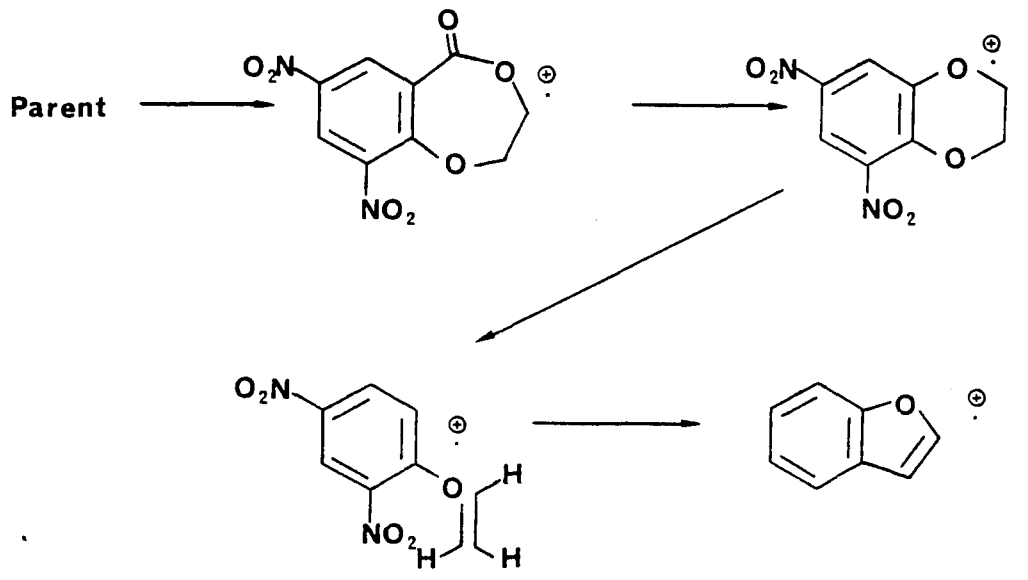


Fig. 16

The lactones 30, 38, and 39, in comparison to the corresponding esters, exhibit a decrease in the carbonyl stretching frequency. In these lactones, the carbonyl

frequency decreases from 1720-1690 cm^{-1} as substituents are placed on the aromatic nucleus.

The acetate derivates, compounds 35, 36, 48, 49, and 50 all exhibit a distinctive stretching region between 1250-1200 cm^{-1}. There are generally three stretches[150, 151] in this region which is in agreement with known values.

The dilactone 32 does show a unique feature in the infrared spectrum. There are two carbonyls observed at 1710 and 1730 cm^{-1}. This doubling of carbonyl absorptions may be attributed to a symmetric and an asymmetric stretch of the ester carbonyls in the 14-membered ring.

Ultraviolet spectroscopy of the esters and lactones of the unsubstitued, brominated and nitrated compounds was used to study what effect ring closure and/or aromatic substitution would have upon the π system. In order to minimize solvent effects, all spectra were measured in methanol solutions. In Table V are compiled the observed data for the six compounds which have been examined.

The first overall trend observed is that the lactones 30, 38, and 39 all absorb at lower energy than the corresponding esters 26, 34, and 40, respectively. A plausible explanation for this observation is that there is more effective π-orbital overlap in the lactones, where the carbonyl is not free to rotate.

A second pattern noted is dependent upon the nature of the aromatic nucleus and its substitution. The order

established, where an increase in energy is needed to excite the system, follows: brominated species < unsubstituted species < nitrated species.

Table I. Characteristic ^1H NMR Chemical Shifts in the Aromatic Region of o-Substituted Benzoic Acids, Esters, and Lactones.

Compound Number	UNH Spectrum numbers	1	2,3 average	1 - 2,3 average
26	7392 $CDCl_3$	7.8	7.25	0.55
27	6070 $CDCl_3$	7.8	7.15	0.65
30	8967 $CDCl_3$	7.9	7.3	0.60
32	9807 $CDCl_3$	7.8	7.15	0.65

Table I. Continued

Compound Number	UNH Spectrum numbers	1	2,3 average	1 - 2,3 average
33	7887 $CDCl_3$	8.1	7.5	0.60
42	7417 Acetone	8.1	7.3	0.80
43	9179 $CDCl_3$	8.0	7.15	0.85
58	6097 $CDCl_3$	8.1	7.3	0.80

Table I. Continued

Compound Number	UNH Spectrum numbers	1	2,3 average	1 - 2,3 average
59	9015 $CDCl_3$	8.2	7.25	0.95

Table II. Characteristic ^1H NMR Chemical Shifts in the Aromatic Region of o-Substituted Benzoic Acids, Esters, and Lactones.

Compound Number	UNH Spectrum numbers	A	B	C	$A - \frac{(B+C)}{2}$
34	10073 $CDCl_3$	7.85	6.85	7.55	0.65
37	6266 $CDCl_3$	8.05	7.2	7.75	0.57
38	8200 $CDCl_3$	8.1	6.9	7.6	0.85
46	9690 Acetone	8.15	7.15	7.65	0.75

Table III. Characteristic ^{13}C NMR Chemical Shifts in the Aromatic Region of Parent o-Substituted Benzoic Acids, Esters, and Lactones.

Compound Number		C_1	C_2	C_3	C_4	C_5	C_6
26	Actual	120.5	159.0	115.2	133.8	121.0	131.5
	Method 1	116.8	159.9	114.8	133.9	121.0	130.5
	Method 3	120.5	159.2	112.3	133.5	120.1	131.6
30	Actual	121.0	154.7	119.3	134.9	122.0	133.5
	Method 1	116.8	159.9	114.8	133.9	121.0	130.5
	Method 2	120.5	159.2	112.3	133.5	120.1	131.6
33	Actual	118.6	158.1	113.9	134.8	122.5	131.8
	Method 1	116.8	160.3	114.7	134.5	120.9	130.9
	Method 2	119.9	156.3	111.1	131.5	118.7	129.2

Table III. Continued

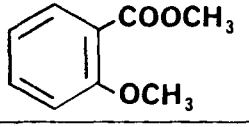
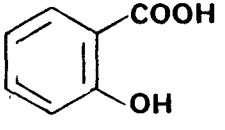
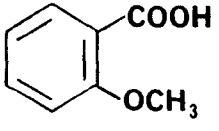
Compound Number		C_1	C_2	C_3	C_4	C_5	C_6
42	Actual	121.7	158.3	114.2	132.4	122.6	133.9
	Method 1	120.5	157.7	114.4	132.1	120.6	128.3
	Actual	120.5	159.2	112.3	133.5	120.1	131.6
	Actual	113.2	161.6	117.2	135.6	119.2	130.5
	Actual	119.9	156.3	111.1	131.5	118.7	129.2

Table IV. Characteristic ^{13}C NMR Chemical Shifts in the Aromatic Region of Polysubstituted Benzoic Acids, Esters, and Lactones.

Compound Number		C-1	C-2	C-3	C-4	C-5	C-6
34	Actual	121.9	157.9	116.7	136.3	112.9	134.0
	Method 1	118.5	158.3	116.5	137.3	115.5	133.9
	Method 2	122.2	157.4	116.9	137.2	115.5	134.9
	Method 3	122.2	157.6	114.0	136.9	114.6	135.0
37	Actual	117.9	158.41	122.8	137.9	113.8	135.1
	Method 1	118.5	158.9	116.4	137.9	115.4	134.3
	Method 2	120.3	156.5	115.6	138.2	117.0	135.2
	Method 3	121.6	154.7	112.8	134.9	113.2	132.6
38	Actual	122.9	153.9	120.4	137.0	114.9	135.9
	Method 1	118.9	158.3	116.5	137.3	115.5	133.9
	Method 2	122.7	153.1	121.0	138.3	116.5	136.9
	Method 3	122.2	157.6	114.0	136.9	114.6	135.0

Table IV. Continued

Compound Number		C-1	C-2	C-3	C-4	C-5	C-6
39	Actual	121.8	151.7	140.4	124.0	142.4	132.2
	Method 1	118.9	160.9	135.7	124.1	141.9	131.5
	Method 2	122.8	155.7	139.9	125.3	142.9	134.5
	Method 3	122.3	160.2	138.0	124.5	142.0	132.0
40	Actual	126.9	155.9	141.4	123.5	144.4	129.5
	Method 1	118.9	160.9	135.7	124.1	141.9	131.5
	Method 2	122.3	160.0	136.1	124.2	141.9	132.5
	Method 3	122.3	160.2	138.0	124.5	142.0	132.0
41	Actual	123.0	156.0	141.6	128.0	144.7	129.5
	Method 1	118.6	161.3	135.6	124.9	141.8	131.9
	Method 2	120.4	159.1	134.8	125.2	143.4	132.8
	Method 3	121.7	157.3	132.0	121.9	139.6	130.2

Table IV. Continued

Compound Number		C-1	C-2	C-3	C-4	C-5	C-6
46	Actual	125.3	157.6	116.8	136.6	113.6	134.9
	Method 1	122.2	156.1	116.7	135.5	115.1	131.7
	Method 2	123.4	156.7	115.8	135.8	117.1	137.3
	Method 3	none					
47	Actual	124.3	161.7	128.3	114.5	142.7	128.6
	Method 1	122.3	158.7	135.5	133.9	141.5	129.3
	Method 2	123.5	159.3	135.1	122.8	143.5	134.9
	Method 3	none					

Table V. UV Absorption Spectra

Compound Number	Wavelength	Molar Absorptivity
30	293	2900
	233	6700
26	287	2400
	229	5200
38	306	1230
	232	5400
34	303	2200
	232	8760
39	282	9600
	215	17750
40	272	12000
	213	21250

PART II. NUCLEOPHILIC AROMATIC SUBSTITUTION IN A DINITROSALICYLIC LACTONE WITH RING OPENING AND ELIMINATION VIA MEISENHEIMER INTERMEDIATES

INTRODUCTION

Nucleophilic aromatic substitution reactions on activated rings containing strong electron-withdrawing groups have been under investigation for many years.[157-160] From investigations of this reaction, classified by Bunnett as S_NAr[161], it has been demonstrated that fluoride is generally the favored leaving group. However, alkoxides and even nitro groups are known to be good leaving groups in nucleophilic aromatic substitution.[162, 163] Nucleophiles used in such studies include sulfur compounds, amines, alkoxy, and various organometallic compounds.

A great deal of evidence has been accumulated in favor of an addition-elimination mechanism in an S_NAr reaction, such as is depicted in Figure 17.

S_NAr Mechanism

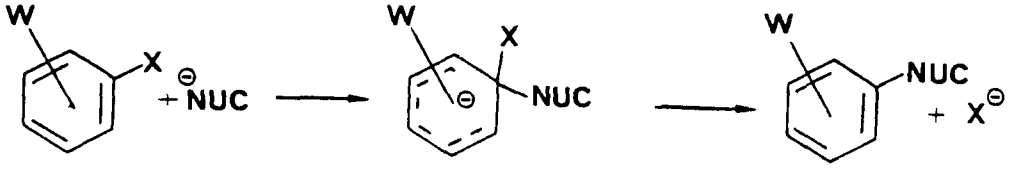


Fig. 17

Occasionally interesting stable and isolable intermediate salts are obtained. These have become known as the Jackson-Meisenheimer or Meisenheimer complexes. The first such intermediate was described by Jackson and Gazzolo, who isolated a brightly colored salt from the reaction mixture of trinitroanisole and sodium methoxide. They proposed a quinoid structure as in Figure 18 for the intermediate.[164] Since the preparation of this first

Quinoid Representation of a Meisenheimer Complex

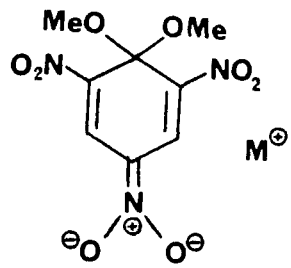
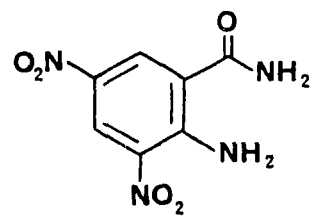


Fig. 18

salt, hundreds of Meisenheimer complexes have been isolated or identified by spectroscopy or other physical methods.[165-170]

The present study was an outgrowth of the original project to prepare and examine macrocyclic lactones. This investigation began with the noted difference in reactivity of the dinitrolactone 39 and the dinitroamide 47 towards aqueous ammonium hydroxide. The dinitrolactone underwent nucleophilic aromatic substitution to afford

iramine (60)[171-173], whereas the dinitrobenzamide 47 was unchanged when subjected to the same reaction conditions.



60

This observation demonstrated a novel ethereal lactone ring opening with the elimination of a β-oxyethyl group.

A goal of this project was to explore the scope of nucleophilic aromatic substitution chemistry in a series of compounds including the dinitro-7-membered ethereal lactone 39 and the corresponding acyclic methyl ester 40. In this way, the effect, if any, of the 7-membered lactone ring and aromatic substitutents could be examined in nucleophilic aromatic substitution.

Various nucleophiles were to be chosen in an attempt to ascertain whether the nucleophile played a major role in the substitution reaction. An additional outcome of this project would be the preparation of novel compounds difficult to synthesize by other known methods.

HISTORICAL

Nucleophilic aromatic substitution has been and continues to be of great interest in organic chemistry. In several excellent reviews, monographs, and specialist reports the various current aspects involved in this area of research are discussed.[157-160, 174, 175]

The three well-defined mechanisms are the S_N1, benzyne, and S_NAr mechanisms. The major emphasis in this thesis will be placed on the theory and discussion of the S_NAr (or activated nucleophilic substitution) mechanism.[161]

The S_N1 reaction usually involves diazonium salts and the decomposition of the salts in the presence of nucleophiles with loss of N_2. It has been demonstrated that the reaction rate is first order, dependent upon the diazonium salt and independent of the concentration of the nucleophile.[176]

The benzyne mechanism was first investigated by J. D. Roberts when it was noted that ^{14}C-labeled chlorobenzene, when treated with potassium amide, afforded two isomeric anilines.[178] Later benzyne was trapped in the presence of anthracene to afford triptycene and has since become a synthetic intermediate in many reactions.[179, 180, 181] Several general methods for

generating benzynes have been developed; among them is the thermal or photolytic decomposition of diazotized anthranilic acid derivatives.[180]

The S_NAr reaction is generally accepted as being a two-step mechanism.[182] An energy diagram for the steps is outlined below (Fig. 19). The kinetics are second order

Energy Diagram of an S_NAr Mechanism

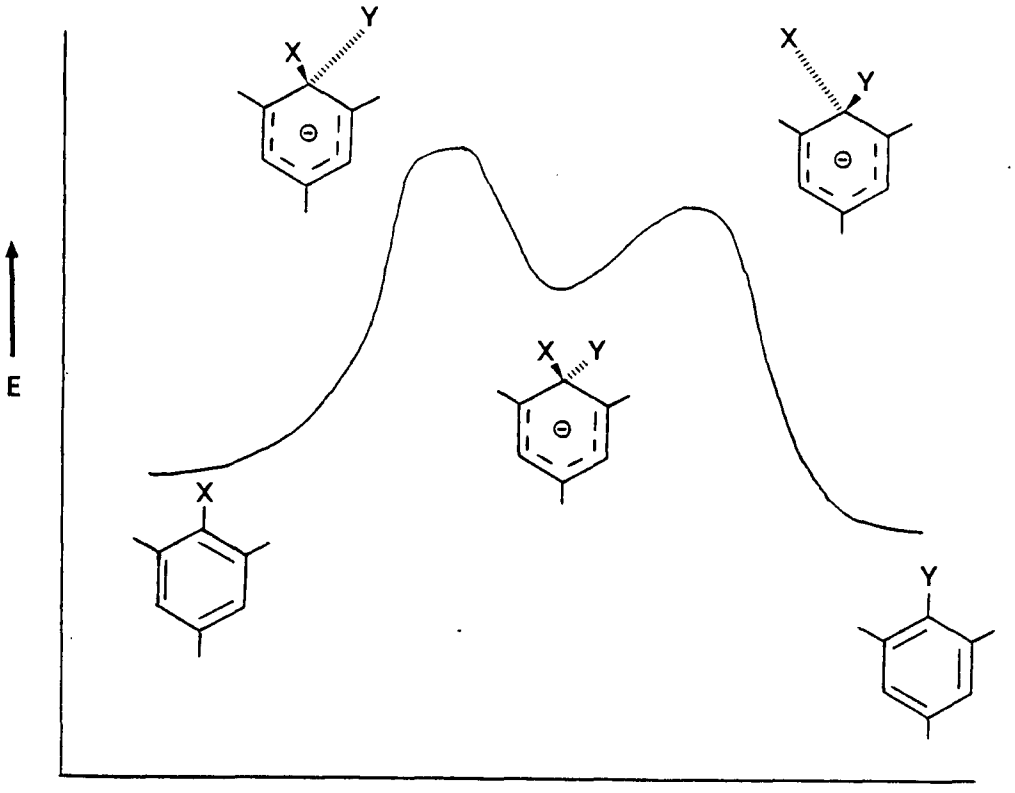


Fig. 19

for the S_NAr reaction; first order for the substrate and first order for the attacking species.

Aromatic nucleophilic substitution reactions are enhanced by the presence of electron withdrawing groups ortho and/or para to the leaving group. The most common

activator is the nitro group, which helps to delocalize some of the negative charge associated with the aromatic nucleus after a nucleophile has attacked.

In general, it has been shown that F > NO_2 > OTs > SOPh > Cl, Br, I > N_3 > NR_3^+ > OAc, OR, SR, SO_2F, NH_2 is the order for leaving groups.[160, 183-185] This depends on each substrate and should only be used as a general guideline. The most interesting point to note is the ability of fluorine and nitro to act as good leaving groups. Several explanations may account for this. Nitro and fluorine groups both have large negative inductive effects which help to alleviate some of the charge buildup on the aromatic system. Another explanation is that fluorine, which can hydrogen bond, does so with hydrogen-bearing nucleophiles,[186, 187] and its removal is thereby facilitated. Another way to think of this is that a strongly electronegative atom, such as fluorine, attached to an aromatic carbon, lowers the transition state energy for the attack of the nucleophile. In fact, it has been calculated that the energy of activation for the fluoride is less than that of the iodide by 4 kcal/mole, which is explained by electronegativity alone.[188]

A point to consider in the S_NAr mechanism is the nucleophile. The effect of the attacking nucleophile varies for each individual substrate, but an overall trend may be considered as a general guideline. Bunnett has arranged a series of nucleophiles, as follows, according

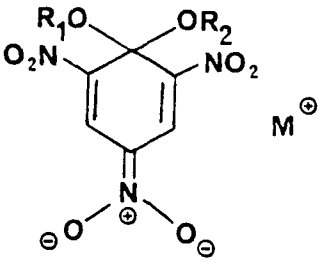
to their abilities to displace halide in nitrated compounds: NH_2^- > Ph_3C^- > $PhNH^-$ > ArS^- > RO^- > R_2NH > ArO^- > OH^- > $ArNH_2$ > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH.[160, 161, 189]

Reaction rates are often dependent on the nature of the solvent. High rates are usually found in dipolar aprotic solvents (DMF, DMSO); methanol, DMSO and water often have a large accelerating effect when added to the solvent system. It is therefore necessary to consider what solvent system is best when a nucleophilic aromatic substitution reaction is desired.[190-195]

When an activated substrate is treated with a nucleophile, several reactions can occur, these being dependent upon the solvent, nucleophile, and substrate structure. Considering the mechanism and the energy diagram Fig. 19, there is a transfer of charge from the nucleophile to the aromatic system. Several types of interactions may occur. A donor-acceptor complex may be formed, where the bonding interactions between the nucleophile and substrate are weak. Another common interaction is the formation of a covalently bonded complex. This may lead to substitution of a leaving group and a new product or the formation of a stable intermediate known as a Meisenheimer or Jackson-Meisenheimer complex. Several reviews have been written on the subject of the Meisenheimer complexes, which include the synthesis, characterization, and kinetic

studies of these stable intermediates involved in the S_NAr mechanism.[158, 159, 165, 167, 175, 188, 196, 197]

The first isolation and characterization of a stable intermediate involved in the S_NAr pathway was described by Jackson and Gazzolo in 1900.[164] They observed that the addition of sodium or potassium alkoxides to picryl ethers resulted in the formation of brightly colored crystalline solid salts. They assigned a quinoid structure as represented in 62 to these compounds.



62

In 1902, Meisenheimer studied alkoxide base interactions with trinitroanisole and trinitrophenetole. He found that, if trinitroanisole was treated with sodium ethoxide or trinitrophenetole was treated with sodium methoxide, the same brightly colored product was obtained (Fig. 20).[198]

Since the original isolation of these first Jackson-Meisenheimer complexes, literally hundreds have been isolated in solid form or observed by kinetic studies, ^1H NMR, or UV experiments. A "stable" Meisenheimer complex is defined as a species which can be observed by

spectroscopic methods or by isolation, and its formation requires the presence of electron-withdrawing groups which

Preparation of the First Meisenheimer Complexes

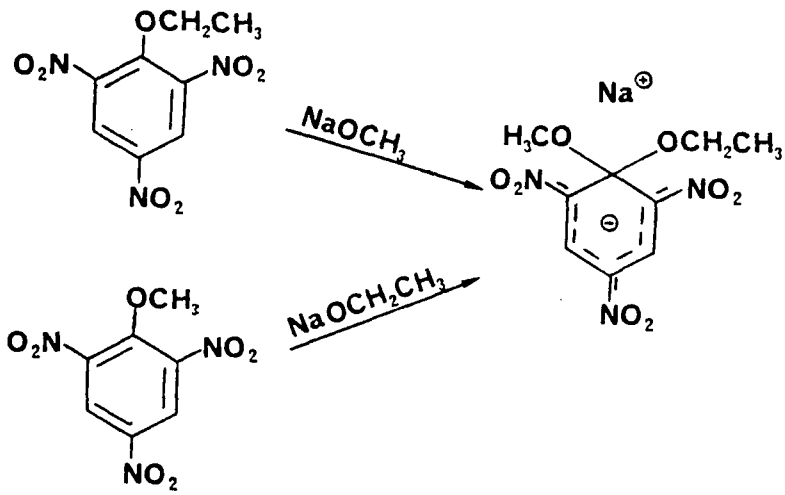


Fig. 20

stabilize the negative charge. Substrates that have been shown to form such stabilized complexes, in addition to the well known polynitrobenzenes, include polycyanobenzenes[199], anthracenes[200], furans[201], thiophenes[202-206], benzofuroxans[207-211], pyridines[212, 213], triazines[214, 215], and selenophanes.[205]

A Meisenheimer complex can be viewed as the result of delocalization of electron density from the incoming nucleophile throughout the π system. A covalent bond created between an incoming nucleophile and the aromatic ring results in the formation of an sp^3 hybrized carbon in the complex. All of the substrates mentioned previously, in some way, can stabilize the negative charge throughout

the π-delocalized system with the interaction of electron-withdrawing substituents.

Meisenheimer complexes are stabilized by two or three nitro groups. However, it has been shown that other electron-withdrawing groups can stabilize the electron charge distribution as well as or better than a nitro group. These include such groups as CN, esters, CF_3, and SO_2CF_3. In a series of papers Fendler has predicted the thermodynamic stabilities of Meisenheimer complexes by correlation of substituent effects.[216, 217]

It has been shown experimentally that the trifluorosulfonate cyclohexadienate complexes form more rapidly and are thermodynamically more stable than the corresponding nitrated analogs. As an example, 1,3,5-tri-(SO_2CF_3) benzene forms the cyclohexadienate complex when treated with neutral methanol (Fig. 21). On the basis of such observations, the trifluorosulfonate is considered a

Trifluorosulfonate Complexes

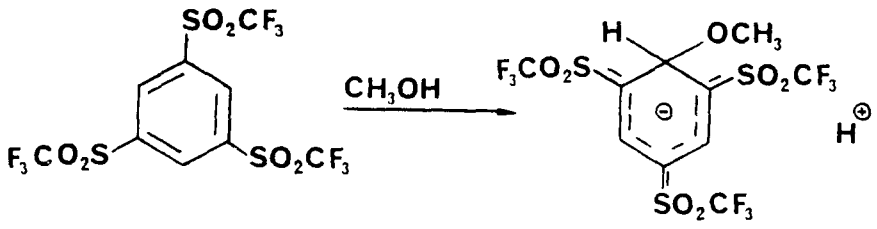


Fig. 21

more highly activating group than a nitro substituent.[218, 219]

The remaining discussion will deal mainly with the polynitrated benzenoid structures. In the literature, these anionic carbocyclic σ complexes are often referred to by several different names. These include cyclohexadienylide, benzenide, cyclohexadienate, and cyclopentadienide.[220-223] The terms Meisenheimer complex and cyclohexadienate will be used in the following material.

In the description of a Meisenheimer complex, an identification system for carbon sites is defined as presented in the following diagram (Fig. 22). The sp^3

Carbon Numbering System of Meisenheimer Complexes

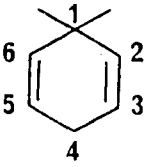


Fig. 22

tetrahedral carbon is always designated as the C-1 carbon; the remaining carbons are then assigned numerical values in a clockwise fashion.

There has been considerable experimental evidence presented to support a structure which is more quinoid in structure than the delocalized system represented below

(Fig. 23). Molecular orbital calculations lend strong support to the quinoid structure 62. From this data, it

Delocalized Representation of Meisenheimer Complexes

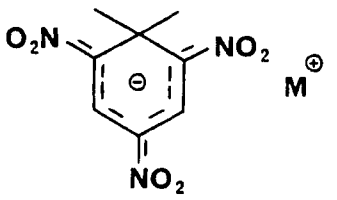


Fig. 23

has been demonstrated that most of the negative charge is located on the nitro-bearing carbon para to the sp^3 carbon at C-1.[224, 225] The X-ray crystal structure of 1, 1-dimethoxy-2,4,6-trinitrocyclohexadienate provides considerable information in support of the quinoid structure.[226, 227] The C-4, N-2 bond which is para to the sp^3 hybridized C-1 carbon is significantly shorter than the C-2, N-1 or C-6, N-3 bond. Therefore, there is a larger amount of negative charge located on the oxygen atoms of the N-2 nitro group. The bond lengths between the C-2, C-3 carbons and the C-5, C-6 carbons are shorter than typical benzenoid bond lengths. The nitro groups ortho to the sp^3 hybridized C-1 carbon are nearly planar. This is in contrast with the known dihedral angle of 62° between the ring and nitro groups in trinitrophenetole.[228]

Methods commonly used to characterize Meisenheimer complexes are UV-Vis, IR, ^{1}H NMR, and X-ray analysis and, more recently, ^{13}C NMR. Meisenheimer complexes are usually brightly colored, often yellow, red, or violet. In solution only a small concentration of such a species is needed for study, usually 10^{-4}-10^{-5} M. The experimenter can often see a color change in the reaction mixture indicative of the presence of a Meisenheimer complex in solution.

Typically, the characteristic UV-Vis has two strong absorptions between 390-600 nm with large extinction coefficients. These extinction values range from 10,000-40,000 units in value and are much stronger than charge transfer bands of aromatic π complexes.[229] These absorptions may be qualitatively explained as electronic transitions between the highest occupied molecular orbital and the lowest unoccupied molecular orbital in the delocalized anion.[230, 231] Absorptions in the visible region are rationalized as charge transfer interactions between the aromatic nucleus and the nitro groups.

UV spectroscopy lends itself well to kinetic studies and for the identification of Meisenheimer complexes. Various solvent systems have been employed in UV experiments including water, DMSO-water, methanol, ethanol, acetone, acetonitrile-water, methanol-DMSO, water-dioxane, and water-DMF. It cannot be predicted with any certainty which solvent will work best for a UV study.

It is known that DMSO and DMSO-water mixtures help to solvate and enhance Meisenheimer complex stability to a great degree. Most kinetic and thermodynamic measurements have been done with DMSO as the solvent system.[232-235]

Another important method for detection of Meisenheimer complexes has been IR spectroscopy. The characteristic stretches observed in these types of compounds are the nitro stretching modes. Typically, the nitro asymmetric and symmetric nitro stretching frequencies lie between 1550-1530 cm^{-1} and 1350-1340 cm^{-1}, respectively.[236] This range is dependent upon the force constant of the N-O bond. If this force constant is decreased by a negative charge, then the N-O symmetric stretch and asymmetric stretch should decrease. Because of this negative charge being present in a Meisenheimer complex, the nitro stretches are shifted to lower values of 1520-1490 cm^{-1} and 1330-1300 cm^{-1}.[237-240]

In 1,1-dialkoxy and 1,1-oxospirocylic Meisenheimer complexes, there are characteristic regions for the C-O-C stretching frequencies. The 1,1-dialkoxy complexes have strong absorptions at 1225-1040 and a weaker one at 1010 cm^{-1}. These stretches do not resemble the parent aromatic ethers but are more similar to bands characteristic of ketals.[241-242]

Two remaining points of interest in the IR spectra are the diminution of the C-H stretch and the shift of the C=C stretch. Typically, the C-H stretch at 3090 cm^{-1} is

very weak, and the usual two C=C stretches between 1630-1420 cm^{-1} are replaced with a single absorption near 1615 cm^{-1}.[238, 240, 243]

^1H NMR has become of great value as an effective method for the determination and comparison of Meisenheimer complexes.[165, 244, 245] The Meisenheimer "aromatic" and aliphatic protons are shifted upfield relative to the parent aromatic compound. As an example, when trinitroanisole is treated with sodium methoxide, the aromatic protons shift upfield from 9.0 ppm to 8.6 ppm. The methyl ether shifts from 4.0 ppm to a more typical aliphatic methyl ether chemical shift of 3.0 ppm.[246, 247] It is interesting to note that the cation has very little if any effect on the chemical shift of the cyclohexadienate compound. If fact, in some instances the cations are not even reported.[248]

In several cases more than one intermediate is involved in an S_NAr reaction. ^1H NMR and UV spectroscopy studies have shown that there is often a competition between kinetic and thermodynamic Meisenheimer intermediates along the pathway of nucleophilic substitution. As an example, it has been shown by ^1H NMR that there is a fast attack at the C-3 carbon of trinitroanisole followed by a slower formation of the more stable 1,1-dimethoxy Meisenheimer (Fig. 24).[247] Formation of transient intermediates has been observed with other similar substrates by UV spectroscopy studies.[249-255]

Kinetic and Thermodynamic Intermediates of Trinitroanisole When Treated with Sodium Methoxide

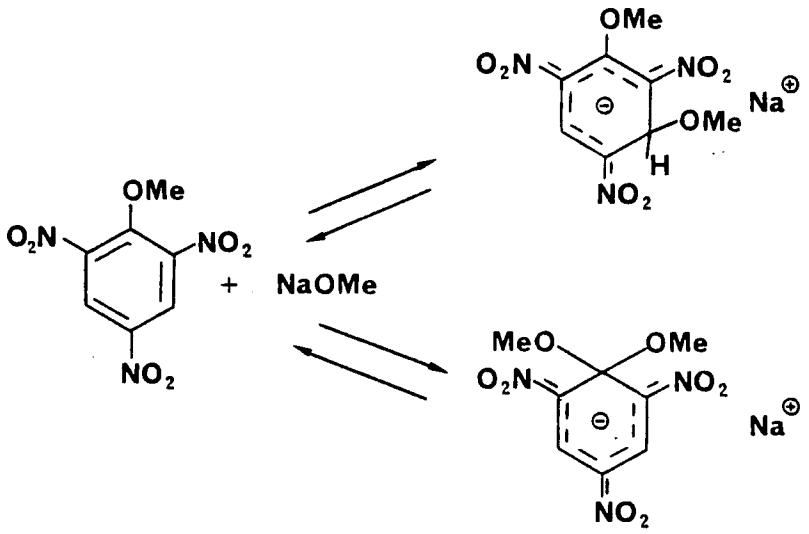


Fig. 24

A more modern approach to discern whether two mechanistic pathways or more than one intermediate is forming in a reaction medium is the use of stopped flow and flow NMR methods. A representative study is the interaction of methoxide with picryl chloride in DMSO. The colored species formed when picryl chloride and methoxide were mixed was assumed to be 63.[256] When the reaction was followed by ^{1}H NMR, however the intermediate observed was actually 64 and not the previously proposed 63.[257]

Gan and Norris approached this mechanistic problem in a different way by using stopped flow UV spectroscopy. They were able to demonstrate that there were two separate mechanistic pathways occurring in the methanol reaction medium.[258] The faster process involved the attack of the nucleophile at the C-3 carbon, and a second slower process involved the attack of the nucleophile at the C-1 carbon. The final product observed in the reaction mixture was the 1,1-dimethoxy Meisenheimer complex 66. This can best be represented by following the reaction scheme (Fig. 25).

Reaction of the Chloro-2,4,6-Trinitrobenzene with Sodium Methoxide

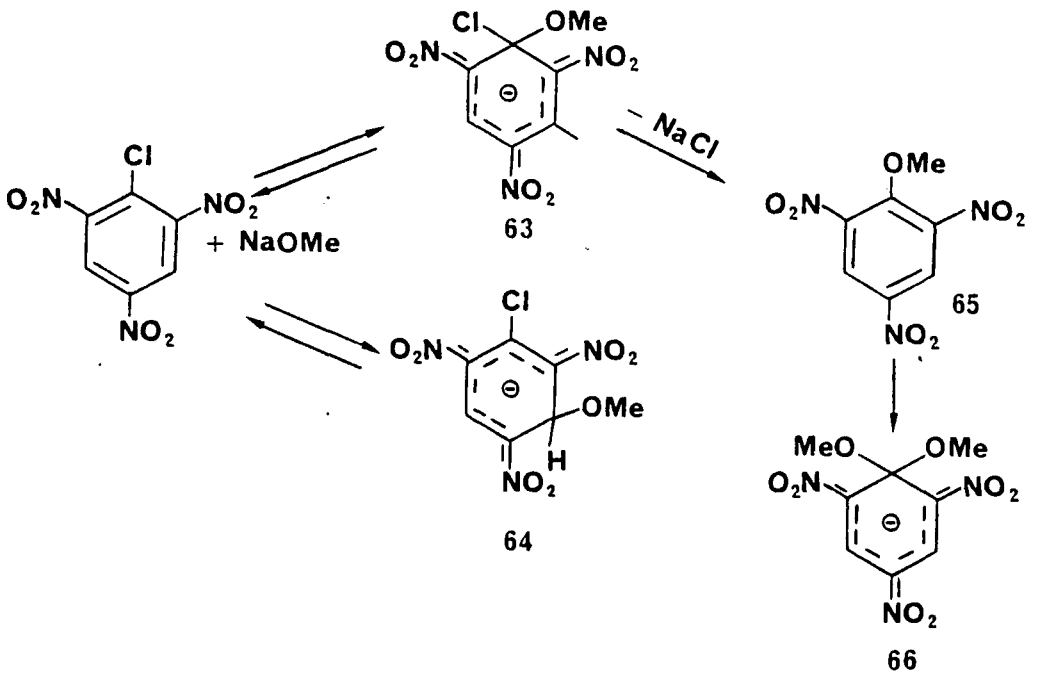


Fig. 25

The results obtained by Gan and Norris were in agreement with some original work by Servis, where ^{1}H NMR spectroscopy was used to study the reaction of sodium methoxide with 2,4,6-trinitroanisole in DMSO.[247, 249] These separate studies help to demonstrate that attack at the C-3 carbon is kinetically favored and the attack at the C-1 carbon, to give the thermodynamic intermediate, occurs through an equilibration process. A more extensive study was undertaken by using a stopped flow technique on chloro, nitro, and methoxy 1-X-2,4,6-trinitrobenzene analogs. Again, the attack of the hydroxide ion at C-1 was found to be a slow process. Kinetic products were detected as unstable intermediates before the attack at the C-1 carbon was observed.[259]

Work by Bunnett, using stopped flow and UV spectroscopy, indicated a two-stage process and formation of an intermediate in the reaction of 1-ethoxy-2,4-dinitronaphthalene and n-butylamine in DMSO-methanol. Bunnett proposed that in the reaction pathway the complex 67 must be formed (Fig. 26). Subsequent loss of ethoxide would then afford the isolated product 68.[260] Fyfe and coworkers reinvestigated the same reaction using flow ^{1}H NMR measurements and concluded the intermediate 67 proposed by Bunnett was indeed formed. From these two independent studies, a reasonable reaction diagram can be outlined to show the proposed reaction mechanism (Fig. 26).[261, 262]

Reaction of 2-Ethoxy-3,5-Dinitronaphthalene with Dibutylamine

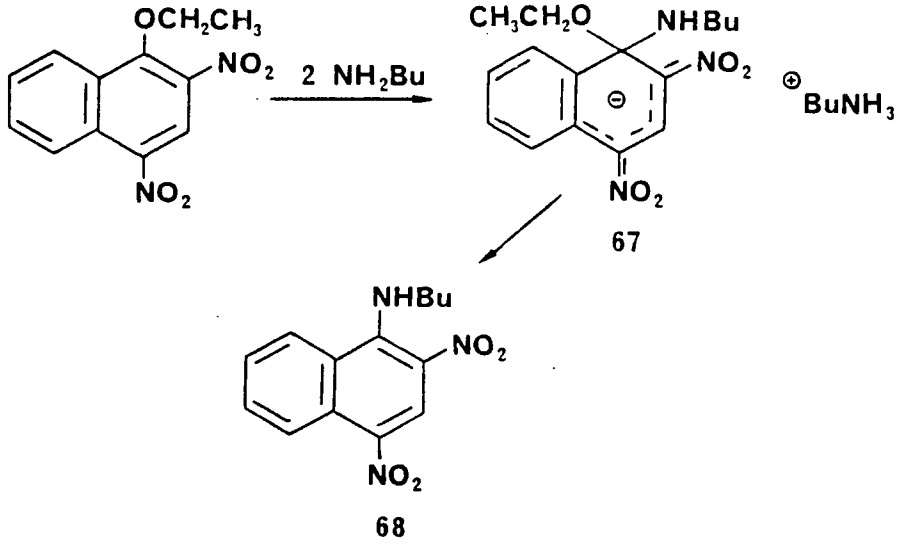
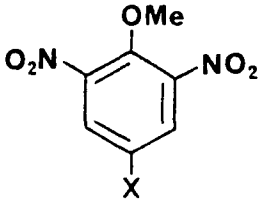


Fig. 26

^{13}C NMR has just recently been introduced as an investigative probe into Meisenheimer structures.[263, 264] Carbon chemical shifts depend on steric and charge distribution effects and provide useful information in structural assignments.[139, 265] However, when substituents are ortho to each other, the additivity relationship breaks down, and the carbon shielding constants reflect the degree of steric hindrance due to electronic interactions.[266] When substituents are not ortho to each other, the additivity relationships are

generally quite good, and the calculated values are within ± 2 ppm of experimental measurements.

Terrier and Olah have examined carbon shifts in the substituted 4-X-2,6-dinitroanisoles 69 or 6-X-2,4-dinitroanisoles 70 and the corresponding 1, 1-dimethoxy cyclohexadienate complexes 71, 72. From these studies, they have found that the calculated chemical shift values



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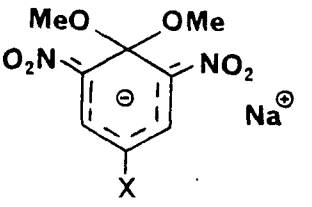

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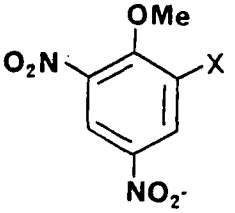

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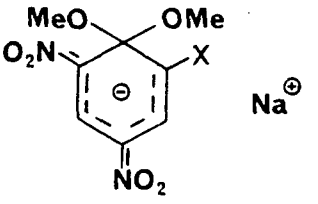


72

for the anisoles, relative to benzene (128.5 ppm), for the C-3 and C-4 carbons are generally in good agreement. However, there are large deviations in the C-1 and C-2 assignments. The C-1 carbon is shifted upfield from the calculated value by approximately 4 ppm. The C-4 carbon is shifted downfield by 9 ppm. These deviations are attributed to the severe steric compression in the ortho nitroanisoles. Because of this compression, the methoxy

group may lie out of the plane of the aromatic system. This has been shown to be true in 2, 6-dialkylanisoles.[266, 267, 268] However, in 2-nitroanisole, 2-X-4,6-dinitroanisole, and 4-X-2,6-dinitroanisole it has been shown from carbon chemical shifts that the methoxy groups lie in the aromatic plane and the ortho nitro groups are twisted out of the plane, a conclusion consistent with the X-ray data for 2,4,6-trinitrophenetole.[228]

When the 1,1-dimethoxy Meisenheimer complexes were studied by ^{13}C NMR, Terrier and Olah both noted several trends. When going from the anisole to the 1,1-dimethoxy complex, both the C-1 and the methoxy carbons were shifted upfield. This is expected for the C-1 carbon because of the hybridization changes from sp^2 to an sp^3 center. The carbon resonances of C-3 and C-5 are shifted downfield relative to the parent anisole, and the C-2, C-4, C-6 are shifted upfield. This is in agreement with molecular orbital calculations which predict that the negative charge should be located at the 2, 4 and 6 carbons. The C-4 shift is found to be the largest from the parent compound to the Meisenheimer complex. These experimental results support the proposal that the position para to the sp^3 hybridized center carries a majority of the negative charge.[225, 269]

The effect of the substrate is also important. There is a large class of compounds known to exhibit the ability

to form Meisenheimer complexes. An important aspect to note is that fused aromatic systems, such as naphthalenes, can better stabilize the negative charge through the aromatic system. This can be equated to the effect of an additional ortho nitro group in a typical benzene system.[252]

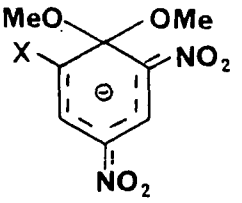
Other effects can alter the stability of the Meisenheimer complex. Solvent and especially the cation play important roles in this stability. It has been shown experimentally that the stability of a Meisenheimer complex in solution is largely dependent on its interaction with the cation. Equilibrium constants for adduct formation are greatly increased by Na^+, K^+, Ba^{2+}, and Ca^{2+} cations and not by Li^+ or tetraalkylammonium ions.[272-274]

In early work, the rate constants of the formation of 1,1-dimethoxy Meisenheimer complexes were found to be dependent upon the concentration of the base or the electrolyte.[213, 222, 254, 275-277] Crampton and Buncel proposed an explanation where the phenomenon was due to ionic association with the counterion. When stability constants were measured for the 1,1-dimethoxy complex of 2-methoxy-3,5-dinitrobenzoic acid, methyl ester and the cation was varied between Li^+, Bu_4N^+, and K^+, there was a dramatic effect noted. The stability constant increased when there was an increase in concentration of potassium methoxide. Because this was not observed with the lithium

or ammonium salts, the classic salt effect could not account for the difference.

To rationalize this, Crampton, Khan, and Buncel proposed that if the cation coordinates better with the complex than the solvent alcohol, the stability constant will increase with the concentration of the cation. If however, the cation coordinates better with solvent than with the Meisenheimer complex, then the stability constant will decrease. It has since been shown that Ba^{2+} and Ca^{2+} form the strongest associations with Meisenheimer complexes. Na^{+} is fairly good and tetrabutyl ammonium salts are very weakly associated.

There is an unusual difference between the association of the cation in spirocyclic "ketal" type complexes when compared to 1,1-dimethoxy analogs. Studies have shown there is no cation stabilizing influence noted in complexes such as 74 or 75. Only in complexes such as 73 is such an influence noted.



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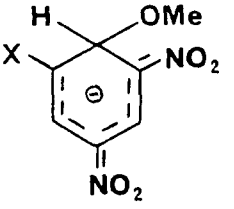

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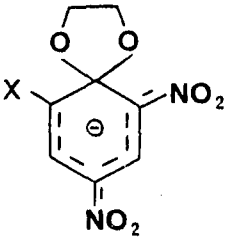


75

It has been proposed that in the 1,1-dimethoxy complexes such as 73, the metal cation is held by the oxygen atoms of the methoxy groups and the ortho

substituents.[272, 274] This is dependent upon the ortho substituents, where esters and nitro groups appear to play a role in this chelation effect. This experimental evidence helps to explain why there is a lower thermodynamic stability for 1,3 complexes than the 1,1-dimethoxy complexes, because of a lack of association with 1,3 complexes.[254, 272, 274, 278, 279, 280]

There has been and continues to be a great deal of interest and intensive research centered on the spirocyclic Meisenheimer complexes. Part of this interest deals with the intramolecular aromatic substitution reaction known as the Smiles Rearrangement.[281-284] A study by Bernasconi and coworkers demonstrates this rearrangement.[285] The formation of the spirocyclic intermediate was noted by UV and ^{1}H NMR spectroscopy (Fig. 27). Equilibria and rates of formation were determined where several intermediates were noted along the pathway to the rearranged product.

There are many well characterized spirocyclic complexes.[229, 286-294] The interest lies in these compounds because they are inherently more thermodynamically stable than their 1,1-dimethoxy analogs and yet are hydrolyzed more readily. Explanations for this contrast proposed thus far include: 1) relief of steric strain after decomplexation; i.e. the spirocyclic system, although thermodynamically favored over the 1,1-dimethoxy system, is more strained. 2) a difference in

the basicity of the leaving group (CH_3O^- and $-OCH_2CH_2O^-$ and 3) stereoelectronic control.[295-297] This last hypothesis has received the most attention. This is best explained in terms of conformational changes and electrostatic interactions.[297]

Smiles Rearrangement

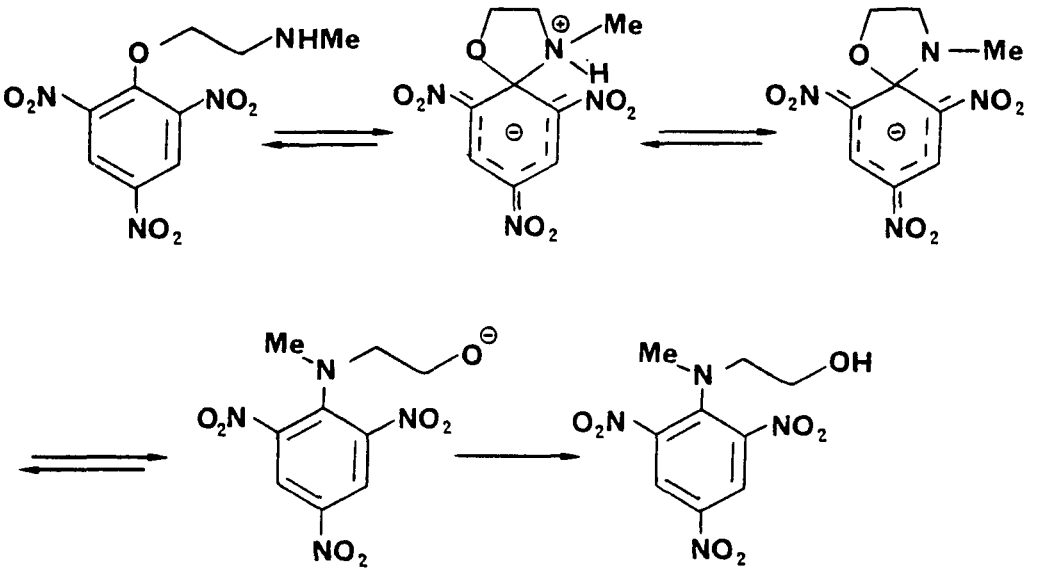
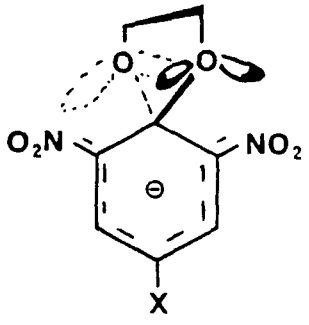


Fig. 27

In the spirocyclic complex 76 the ring adopts the conformation shown. However, for the 1,1-dimethoxy analogs there are three major conformations to be considered. These are pictured as 77, 78, and 79, where 77 is analogous to the spirocyclic complex with the methyl

groups "up" and eclipsed. In 78 both methyls are "down", and in 79 one methyl is "up" and one methyl is "down". Even though 79 would seem to be favored and 78 disfavored because of the anomeric effect, it appears from rate studies and X-ray analysis that 78 is actually the preferred conformation.[226, 273, 274, 297]

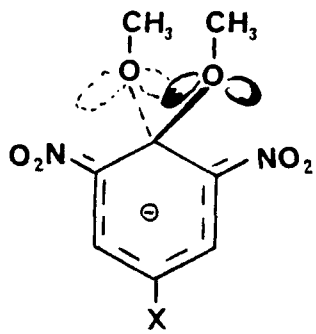
To account for the experimental results, Bernasconi and Crampton have offered a possible explanation as to why, even though the spirocyclic Meisenheimer complexes are thermodynamically more stable, they are hydrolyzed more readily than the 1,1-dimethoxy analogs based on rate and equilibrium constants. They have invoked the use of stereoelectronic control.[295-297] In the past, this explanation has been advanced to account for the



76

hydrolytic breakdown of the tetrahedral intermediates of esters, amides, and acetals. In stereoelectronic control, the hydrolysis of such compounds is facilitated when the lone pair of electrons on a second oxygen or nitrogen is

anti-periplanar to the departing group.[298-301] Since the Meisenheimer complexes are in fact ketals, this stereoelectronic control should play a role in the breakdown of the complexes. In the spirocyclic complexes, the conformation 76 is already nearly anti-periplanar in arrangement, but in the structure 78 the CH_3 is anti-periplanar to the C-O bond being cleaved. The proper alignment of the lone pair electrons and leaving group is available in 79 when the methoxy group pointing down is the leaving group. Thus the spirocyclic complexes are already predisposed to react under hydrolysis conditions, whereas in the 1,1-dimethoxy complexes there must first be a shift in equilibrium from 78 to 79. No matter what the conformational equilibrium between 78 and 79 is, the absence of rotation in the spirocyclic complexes would enhance stereoelectronic control in their hydrolysis.



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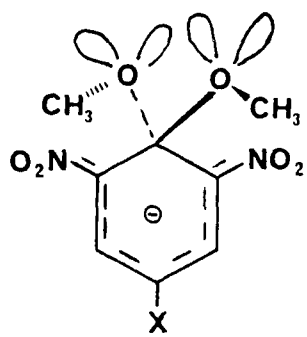

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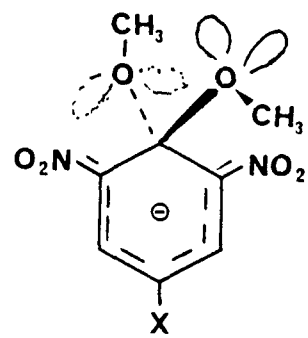
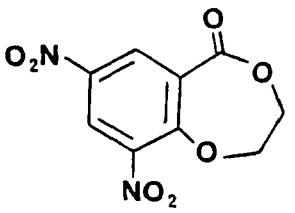


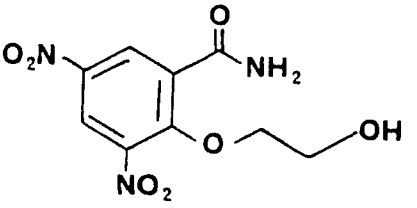
79

DISCUSSION OF RESULTS

Some unexpected results in the first project in the preparation of macrocyclic lactones prompted an investigation into the study of nucleophilic aromatic substitution. Experimental evidence indicated an unusually marked reactivity difference between the dinitrolactone 39 and the dinitroamide 47. When the



39



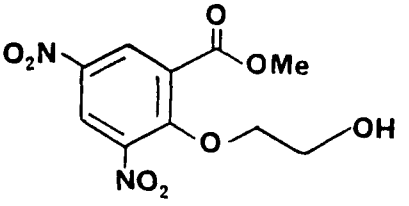
47

dinitrolactone 39 was heated in the presence of aqueous ammonium hydroxide, a reaction took place which afforded iramine (61). This was in contrast to the decreased reactivity of the dinitroamide 47, which did not react with aqueous ammonium hydroxide under any reaction conditions. Neither 39 nor 47 reacted with ammonia at room temperature. This difference in reactivity was somewhat unexpected for two such similar compounds.

Several factors which might play a role in these observations were considered. First, the effect, if any,

of the amide functionality in comparison to the lactone; second, some intrinsic property of the 7-membered ethereal lactone that enhanced nucleophilic aromatic substitution; third, the function that nitro groups may play in the nucleophilic aromatic substitution. A series of experiments to test the possible importance of these factors were planned.

It was decided that the first two factors could be examined by choosing the dinitro methyl ester 40 as a model compound. In 40 the amide functionality of 47 would be changed to resemble that of 39, but at the same time, the ring of 39 is no longer present.



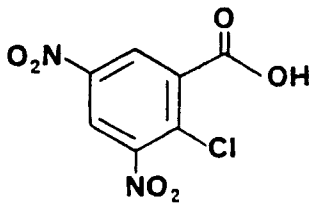
40

To carry out this comparison, the dinitrolactone 39 and the dinitro methyl ester 40 would be subjected to various nucleophiles. These agents included I^-, OH^-, NH_3, $NH(CH_3)_2$, NH_2CH_3, CN^-, enolates, thiophenoxide, $S_2O_3^-$, or 2- SCN^-, and $(NH_4)_2S$.

The outcome of several experiments in this comparative study was the realization that both ester and lactone undergo nucleophilic substitutions under a variety

of conditions. The S_NAr products from the dinitro methyl ester 40 and the dinitrolactone 39 are enumerated in Figure 28. Under each "product" are the letter(s) E or L, denoting whether the "product" was prepared from the dinitro methyl ester 40 or the dinitrolactone 39 as substrate. A general feature in all of the compounds should be noted however; that is, none of the final products contain the β-hydroxyethyl ester. This result in itself led to several questions which will be discussed at a later point.

Because of the loss of the β-hydroxyethyl fragment in the course of the substitution, the structures of several of the products could be confirmed by independent synthesis from 80 with appropriate nucleophiles.

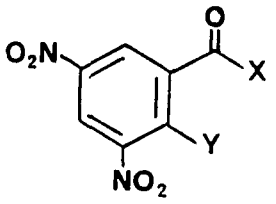


80

Aqueous sodium hydroxide was chosen for an initial experiment.

Products of Nucleophilic Substitution from

Ester(40) or Lactone(39)

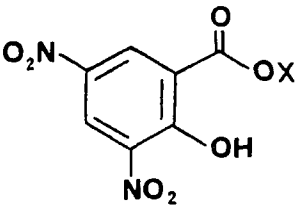


		X	Y
(E,L)	82	OH	OH
(E,L)	84	OH	Sϕ
(E,L)	61	NH_2	NH_2
(E,L)	85	$NHCH_3$	$NHCH_3$
(E,L)	86	$N(Me)_2$	$N(Me)_2$
(L)	87	$O^{\ominus}, \overset{\oplus}{N}H_3\phi$	NHϕ
(E,L)	90	OH	OMe

Fig. 28

When either the dinitrolactone 39 or the dinitro methyl ester 40 was treated with varying amounts of aqueous sodium hydroxide, a bright yellow salt was obtained in

quantitative yields. Reaction conditions were varied as to the amount of base, temperature, and time. In all cases, with either a carbon dioxide or concentrated hydrochloric acid workup to neutralize the reaction solution, the same material was obtained and identified as the mono-sodium salt of dinitrosalicylic acid 81. This



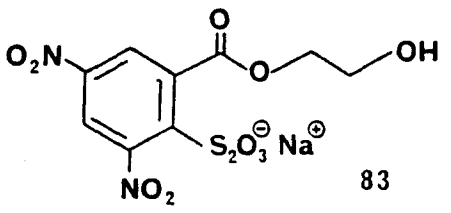
81 X = Na

82 X = H

could be converted to the free acid by treatment with concentrated sulfuric acid in a minimal amount of water. After purificaiton, the acid 82 was obtained in good yields, with spectral and melting point data corresponding to the known substance prepared from 80.[302, 303]
The dinitroacid 41 was obtained from the dinitrolactone 39 when one equivalent of aqueous sodium hydroxide was used, but the result could not be reproduced.

Sodium thiosulfate was tested as a nucleophilic agent on the dinitrolactone 39. The thiosulfate ion is known to be a potent nucleophile in aromatic substitution chemistry.[160] It was envisioned that the thiosulfate would attack the aromatic ring and afford a Bunte-type

salt 83.[304] Bunte salts are readily functionalized and could lead to various possibilities for the synthesis of



83

sulfur containing compounds.[305, 306] It is also known that several Bunte salts exhibit bacteriostatic activity.[307, 308]

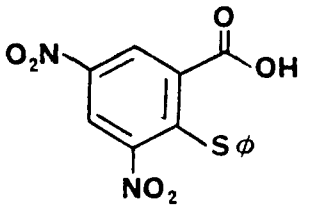
Reaction of the dinitrolactone 39 with sodium thiosulfate under various conditions with ethanol/water afforded only the recovered dinitrolactone 39 in quantitative recovery. No further work was pursued with sodium thiosulfate as a nucleophile.

Several attempts to effect nucleophilic aromatic substitution on the dinitrolactone 39 with "sulfide" nucleophiles were made. When reactions were carried out on the dinitrolactone 39 with preformed NaSH in absolute ethanol, the reaction mixtures darkened immediately; and TLC information showed the disappearance of the dinitrolactone 39. The dark tarry mixtures were subjected to preparative TLC or flash chromatography to afford several fractions, but each consisted of several components according to TLC. When dry H_2S was passed

through an ethanolic solution of dinitrolactone 39, no reaction occurred, and the dinitrolactone 39 was recovered quantitatively.

An alternative sulfur nucleophile, ammonium sulfide, with the dinitrolactone 39 led to confusing results. When the dinitrolactone 39 was treated with aqueous ammonium sulfide at room temperature, no identifiable materials could be isolated. Heating of the aqueous mixture caused formation of black tars, and acidification of any of the solutions afforded polymeric sulfur compounds. A competing reaction may be reduction of the nitro groups, inasmuch as ammonium sulfide is an effective reducing agent for nitro groups.[309, 310] IR spectra of some of the crude materials isolated do exhibit what appear to be NH_2 stretches. Because of these complications, the use of sulfide as a nucleophile was abandoned.

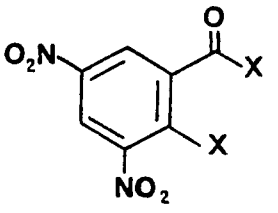
Next thiophenoxide as a nucleophile was examined. When the dinitrolactone 39 was treated with one equivalent of thiophenol and sodium bicarbonate, no reaction occurred; but the use of one equivalent of pregenerated potassium thiophenoxide in methanol at reflux temperatures afforded the 2-thiophenoxy compound 84 in low yield after acidic workup. Identical reaction conditions were used with the 2-chloro-3,5-dinitrobenzoic acid 80 to synthesize the same compound 84 for comparison, the product being formed in high yield. Reaction of the dinitrolactone 39



84

or the dinitro methyl ester 40 with two equivalents of preformed potassium thiophenoxide at reflux temperatures afforded 84 in quantitative yields.

Ammonolysis of the dinitrolactone 39 and the dinitro methyl ester 40 with aqueous ammonium hydroxide, aqueous methylamine, and aqueous dimethylamine led to the corresponding amino amides 61, 85, and 86 in good yields.



61 $X = NH_2$

85 $X = NHMe$

86 $X = N(Me)_2$

Iramine (61) had been reported in the literature. It was demonstrated in several of these reports that iramine and sulfonated analogs exhibit anticoccidiostatic activity.[171-173]

The monomethylated amine 85 had been synthesized by Mori and the crystal structure examined.[311] It was shown

by X-ray crystallography that the aromatic ring is distorted to a boat shape because of steric crowding. From the crystal structure, it appears that intramolecular N-H-O (nitro) and intermolecular C-H (ring) O (nitro) hydrogen bonding is important. Although conclusions about solution behavior need not parallel those from the solid state, this may help to explain why there is a complex splitting pattern in the aliphatic portion of the ^{1}H NMR spectrum and also why three methyl signals are detected by ^{13}C NMR spectroscopy.

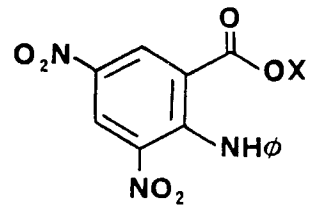
Preparation of dimethylamide 86 has been described by Chen and coworkers.[312] Their method of preparation of dimethylamide 86 was to reflux 2-chloro-3,5-dinitrobenzoic acid 80 in DMF. However, the physical properties do not correspond to the material prepared in this laboratory. Chen's elemental analysis was low in hydrogen; the reported IR, MS, and melting point do not correspond with those obtained in this laboratory. Additional evidence to support structure 86 for the compound isolated in this laboratory comes from the ^{1}H NMR and ^{13}C NMR spectra. Figure 29 shows some of the major differences between 86 and the compound isolated by Chen.

Comparison of Physical Properties for "Dimethylamide" 86

	Chen	Present Work
mp	72-73°	107-109°
Anal. Calcd. for $C_{11}H_{14}N_4O_5$:		C, 46.81; H, 5.00; N, 19.85.
Found	C,46.98; H,4.41; N,19.85	C,46.87; H,5.00; N,19.68
MS	282, 211, 194, 164	282, 190, 146, 102
IR	1600, 1574, 1380	1650, 1540, 1335
^{1}H NMR	none	8.7-8.1 dd, 2 3.2-2.95 4 CH_3's
^{13}C NMR	none	167.78, 147.94, 141.11, 138.51, 132.33, 128.04, 123.94, 42.59, 38.56, 34.92

Fig. 29

Somewhat different results were observed with aniline as a nitrogen nucleophile. When a mixture of the dinitrolactone 39 and aniline was heated to 100°, a black tar resulted. When the dinitrolactone 39 was treated with aniline in refluxing ethanol, the product identified after careful isolation and purification was the 2-anilino-3,5-dinitrobenzoic acid, anilinium salt 87. To confirm this structure, the identical compound was prepared from 80. IR, ^{1}H NMR, ^{13}C NMR, and melting point data were identical for both compounds. Acidification of the salts gave the known 2-anilino derivative 88.[303]



87 $X = \overset{\oplus}{N}H_3\phi$

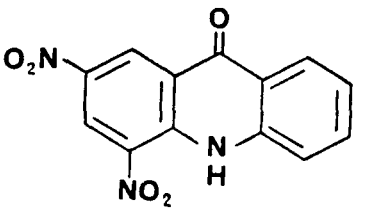
88 $X = H$

The isolation of the anilinium salt lends support to the view that the nucleophile attacks the aromatic nucleus first, before reaction at the carbonyl functionality in either 39 or 40. This is consistent with the earlier observation that the amide 47 is resistant to attack by ammonia. This decrease in reactivity may be attributed to deactivation of the aromatic ring. In the case of the dinitro amide 47, the aromatic nucleus may be somewhat deactivated by the presence of the amide as compared to the ester. An ester functionality but not an amide has been equated to a nitro group in its activating effect.[160]

It should be noted that the aliphatic amines tested afforded nucleophilic aromatic substitution and ammonolysis of the carbonyl functionality. This is in contrast to aniline, a poorer nucleophile, which afforded the S_NAr product with loss of the β-hydroxyethoxy unit in a different manner than the aliphatic amines. It appears that ammonolysis of the resulting β-hydroxyethoxy unit was not as rapid as the loss of the "ethylene oxide"

unit to form the carboxylate. It must also be noted that in order for the aniline displacement reaction to occur, elevated reaction temperatures were required. This is in contrast to the aqueous aliphatic amine displacements, which occurred rapidly at room temperature. One additional point is that the aliphatic amine reactions were all carried out in an aqueous medium, whereas the aniline reaction was performed in ethanol.

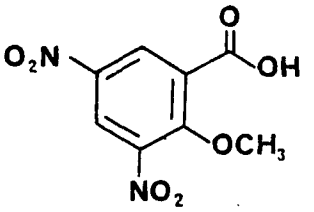
As a sidelight, ring closure of the aniline carboxylic acid 88 to the acridone 89 was explored because of reported antifungal and bacteriocidal activity of these compounds.[313-315] Cyclization with PPA led to the known acridone 89.[316]



89

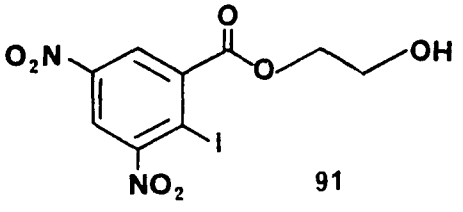
Treatment of either the dinitrolactone 39 or the dinitro methyl ester 40 with excess sodium methoxide at reflux temperature resulted in the formation of 90 after aqueous acidification. Comparison of the material isolated from either reaction mixture with an authentic sample prepared from 80 proved they were identical. In spite of careful acidification and variation in reaction

times, in no case was it possible to isolate a compound with the β-hydroxyethyl ester group intact.



90

All attempts to synthesize the 2-iodo compound 91 from the dinitrolactone 39 met with failure. Reaction conditions were varied where NaI/acetone and NaI/DMSO were employed at various temperatures. TLC information indicated only the presence of dinitrolactone 39, which could be recovered quantitatively after aqueous workup. The ineffectiveness of iodide to displace the ethereal lactone was not totally unexpected, for iodide is known to be a poor nucleophile in S_NAr reactions.[305, 317]



91

It does not appear that the 7-membered lactone ring in 39 shows any added effect when compared to the dinitro methyl ester 40. Both the dinitrolactone 39 and the dinitro methyl ester 40 reacted with nucleophiles in similar fashion.

In no case, was the β-hydroxyethyl ester isolated, even though this was the expected result at the outset of the investigation. A survey of the literature showed that ethylene glycol monobenzoates are hydrolyzed in base considerably faster than the corresponding methyl or ethyl esters. The explanation put forth to account for this is that there is anchimeric assistance associated with the glycol ester. This could explain why the β-hydroxyethyl ester was not isolated under a variety of basic conditions (Fig. 30).[318-321]

"Base Hydrolysis of Ethylene Glycol Monobenzoates"

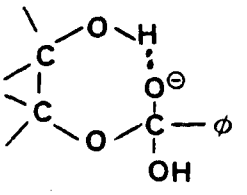


Fig. 30

In the case of the amides, 61, 85, 86, the ester apparently underwent ammonolysis after nucleophilic

aromatic substitution had taken place. However, the aniline product 87 was isolated as the anilinium salt 87. This could occur by the formation of a Meisenheimer complex which would then lose an equivalent of ethylene oxide. This explanation may also be applied for the methoxide and thiophenoxide reactions, where the carboxylic acid is isolated (See Figure 31). Upon aqueous workup, there may be a rapid hydrolysis of the β-hydroxyethyl ester. Further support for this will be provided in the following section.

The original goal to evaluate the role of various activating groups in the nucleophilic aromatic substitution was thwarted by the problem of synthesis. Attempts to mononitrate the monolactone 30 met with failure. Nitrations under varying conditions either afforded the recovered starting material or the dinitrolactone 39. As for the uniqueness of the monolactone 30 or the ester 26 without the activating groups, no nucleophilic aromatic substitutions were observed to occur. A representative example is the ammonolysis of 26, 30, or 42 which afforded the amide 42.

"Nucleophilic Attack on Dinitrolactone 39"

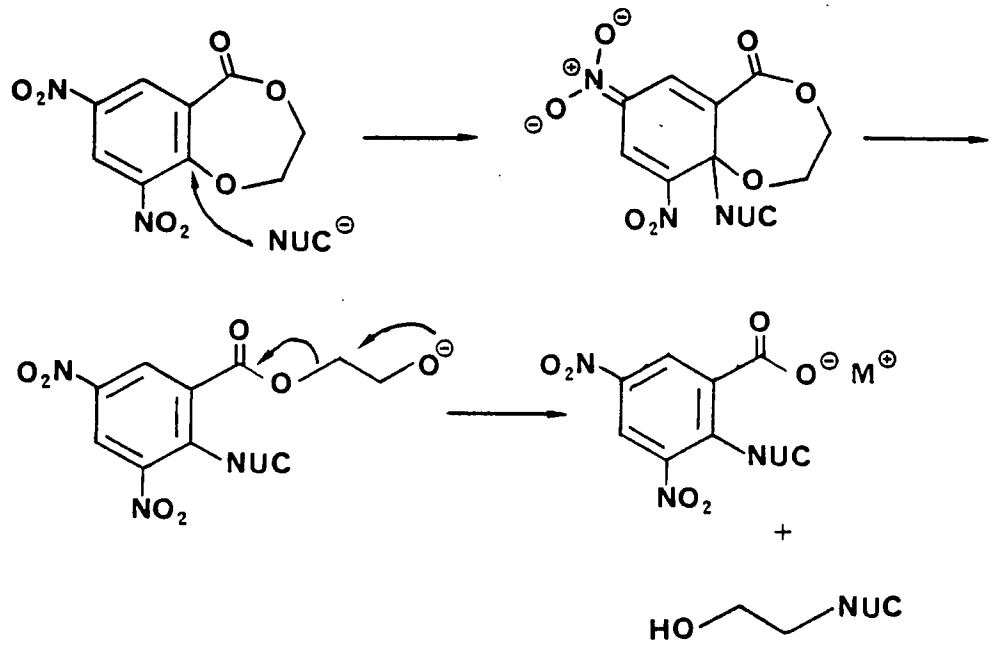
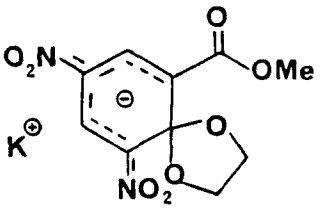


Fig. 31

In light of the experimental results, several new questions were raised as to the sequence of steps and the nature of any intermediates in these nucleophilic reactions. Careful reexamination of several nucleophiles was therefore undertaken.

The results with potassium thiophenoxide depend upon the ratio of nucleophile to substrate and the temperature of the reaction mixture. If the dinitrolactone 39 was treated with an excess of potassium thiophenoxide in refluxing methanol, the 2-thiophenoxy compound 84 could be

obtained in greater than 90% yields after acidic workup. It was found that treatment of the dinitrolactone 39 with one equivalent of potassium thiophenoxide in methanol at room temperature afforded a yellow salt. This salt was identified as the spirocyclic Meisenheimer complex 92 by ^{1}H NMR, IR, ^{13}C NMR, and UV spectroscopy.



92

The ^{1}H NMR of 92 exhibited the characteristic upfield shift from the parent aromatic dinitrolactone 39 from a doublet of doublets centered at 9.0 ppm to a doublet of doublets centered at 8.25 ppm. The spirocyclic methylenes appear as a singlet at 4.5 ppm. This unexpected equivalence has been noted in other spirocyclic Meisenheimer complexes as well.[288]

A possible explanation for this observation is that there is an equilibration process occurring in the NMR solvent whereby the spirocyclic Meisenheimer complex is opening and closing rapidly on the NMR time scale. This would in effect make the methylenes equivalent. The absence of aromatic proton signals in the ^{1}H NMR spectrum

would require that the equilibrium concentration of the benzoate is very small.

Examination of the IR showed a shift of the nitro region to 1520 and 1330 cm^{-1} typical of a Meisenheimer complex.[236-240] The ketal linkage also exhibited a unique pattern in the IR between 1300-1200 cm^{-1}.[241-242] ^{13}C NMR supported the structural assignment as well. Olah and Terrier have shown that in 1, 1-dimethoxy Meisenheimer complexes, the sp^3 carbon is shifted upfield from the parent aromatic compound, and the carbon that is para to the sp^3 center is shifted downfield.[263, 264] This was consistent with the structural assignments for the dinitrolactone 38 and the Meisenheimer complex 107. The ketal methylene carbons appear as a singlet at 69 ppm. Mass spectral information showed that the base peak was that of the dinitrolactone 38 with a m/e of 254.

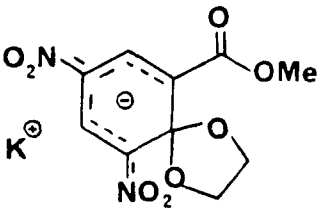
UV-Vis spectroscopy with methanol as solvent showed only weak absorptions at 388 and 475 nm. Addition of a small amount of base increased the intensities of these absorptions considerably. This enhancement of absorption by the addition of base is very typical of Meisenheimer complexes.[165-167] When the solvent was changed to acetone, strong absorptions were noted at 388 and 475 nm even without the addition of base.

A possible explanation is put forth to account for these observations with thiophenoxide. Because of steric interactions, the attack by thiophenoxide at the lactone

carbonyl of the dinitrolactone 39 is competitive with attack at the aromatic nucleus. This is followed by the cyclization of the alkoxide to the intermediate thioester Meisenheimer complex, which is then hydrolyzed by methoxide or methanol to regenerate thiophenoxide or thiophenol and the spirocyclic Meisenheimer complex 92. (See Fig. 32) When the dinitro methyl ester 40 was treated with one equivalent of potassium thiophenoxide in methanol at room temperature, the same spirocyclic Meisenheimer complex 92 was obtained in high yields.

In separate experiments it could be demonstrated that the spirocyclic Meisenheimer complex 92, when treated with one equivalent of potassium thiophenoxide/methanol at reflux temperature, is converted to the nucleophilic aromatic substitution product 84. A possible explanation for this result would be a series of steps beginning with equilibration of the spirocyclic Meisenheimer complex 92 to the open aromatic form. The alkoxide could then attack the ester and displace methoxide, with regeneration of the original lactone. Thiophenoxide could then attack the aromatic nucleus and displace the alkoxy side chain (See Fig. 33), the β-alkoxyethyl group being lost.

S_NAr Attack on Dinitrolactone by Thiophenoxide at Ambient Temperature



92

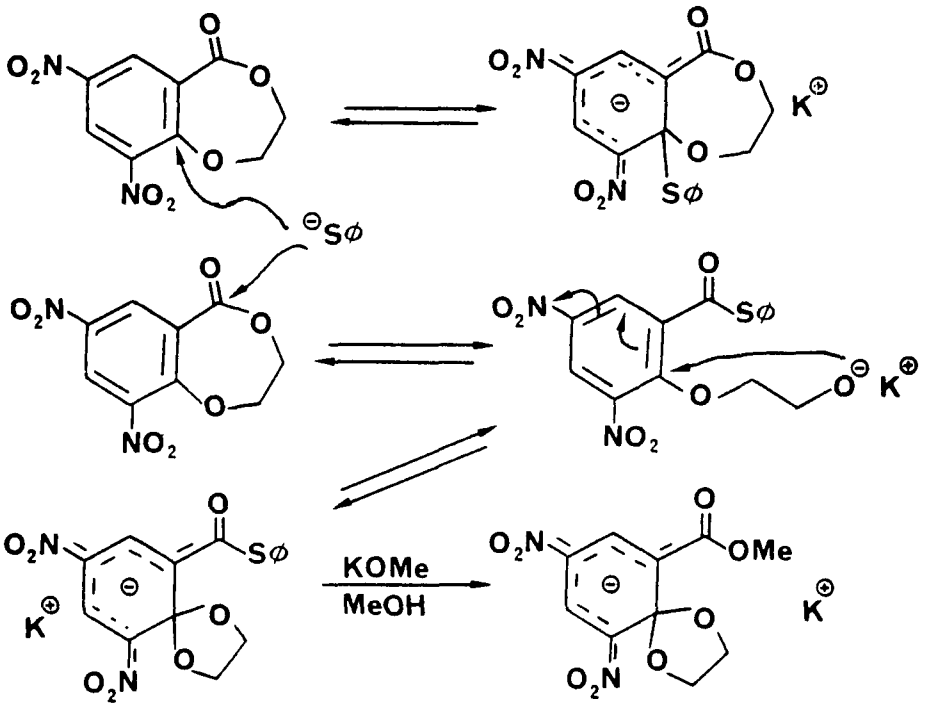


Fig. 32

"Formation of 2-Thiophenoxy 3,5-dinitrobenzoic Acid from the Spirocyclic Meisenheimer Complex 92"

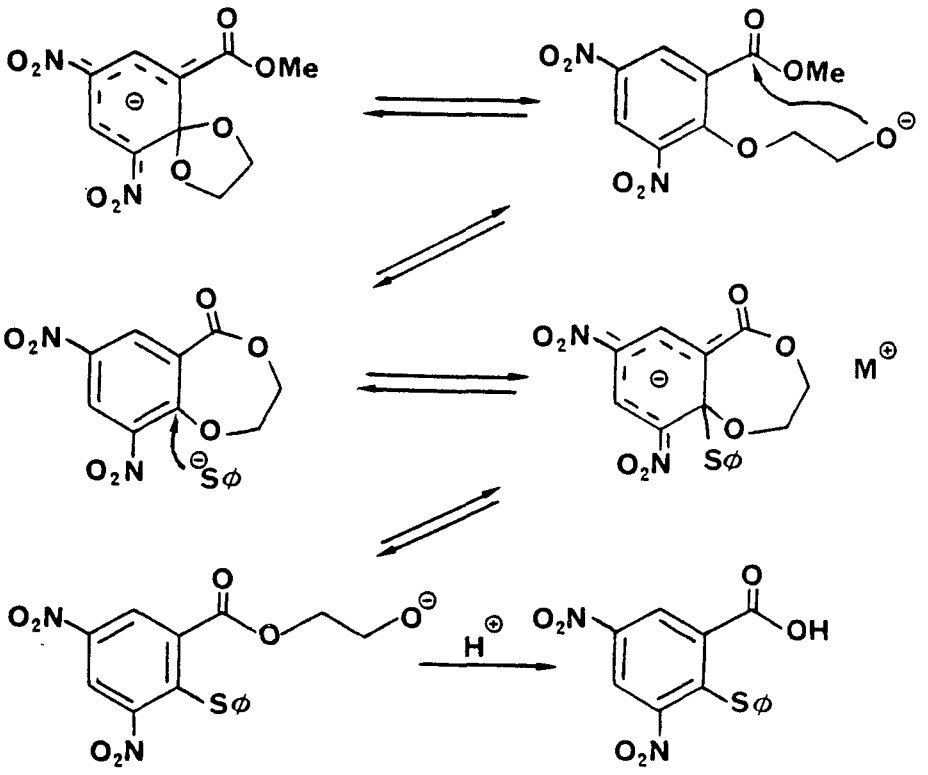


Fig. 33

The same spirocyclic Meisenheimer complex 92 was isolated from dinitrolactone 39 or ester 40 and one equivalent of potassium cyanide in methanol. It is proposed that, because of the low solvation of the cyanide ion, alcoholysis of the ion generates methoxide ion, in spite of the unfavorable equilibrium. The methoxide, once generated, then attacks the lactone carbonyl, which affords the spirocyclic Meisenheimer complex 92 (See Fig. 34).

Formation of the Spirocyclic Meisenheimer Complex 92
by Alcoholysis of Cyanide Ion

$$KCN + MeOH \longrightarrow HCN + KOMe$$

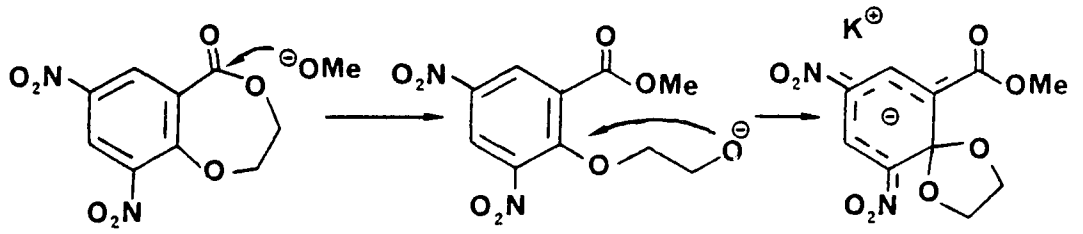


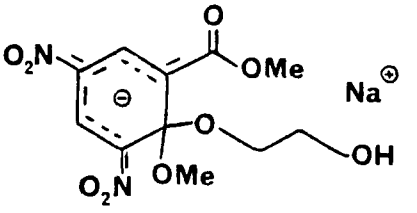
Fig. 34

This competition between cyanide and methoxide has been noted by Gan and Norris in their studies of cyanide attack on trinitro benzenes.[322] It has been demonstrated by Buncel and Norris that the best solvent for cyanide attack on an activated aromatic ring is t-butyl alcohol. The ineffectiveness of cyanide as a nucleophile is attributed to poor solvation of the anion.[323]

Because of the ease of formation of the spirocyclic Meisenheimer complex 92, the effects of various nucleophiles on the complex were examined. Treatment of the spirocyclic Meisenheimer complex 92 with thiophenoxide at reflux has already been described. In a similar way the complex 92 was converted to corresponding nucleophilic aromatic substitution products 61, 82, 85, and 90 when treated with ammonium hydroxide, hydroxide, aqueous methylamine, and methoxide. In each case, the

transformation of the Meisenheimer complex 92 to the substitution product required reflux temperatures. This generation of several nucleophilic aromatic substitution products from a single Meisenheimer complex has, to the best of our knowledge, never been reported before.

Treatment of the spirocyclic Meisenheimer complex 92 with excess sodium methoxide/methanol at room temperature led to a surprising result. A bright orange salt was obtained in quantitative yields. This salt appeared to be the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex 93 by elemental analysis and IR spectroscopy, although the ^{1}H



93

NMR and ^{13}C NMR spectra did not correspond to the structure 93. Furthermore, the MS of this compound did not show the same fragmentation pattern as that of the spirocyclic Meisenheimer complex 92.

The ^{1}H NMR and ^{13}C NMR spectra of 93 in acetone or DMSO and the UV-Vis spectrum in acetone were identical to those of the spirocyclic Meisenheimer complex 92. The only difference in the ^{1}H NMR and ^{13}C NMR was the addition of a methyl peak. At first it was thought that this

material was the spirocycle 92 with a solvated methanol. Repeated recrystallization from ethanol and heating for several days at 100° at reduced pressure did not change the elemental analysis or the IR spectrum. The IR consistently contained an alcohol OH stretch. Placing a sample of the spirocyclic Meisenheimer complex 92 in methanol at room temperature or at reflux did not change its ^{1}H NMR or IR spectrum to that of 93. Because it is known that spirocyclic Meisenheimer complexes are thermodynamically favored species, an experiment was designed to test for the conversion of 93 to 92.

The complex 93 was treated at room temperature with acetone, a solvent used for the NMR spectra. After removal of the solvent and proper drying was accomplished, the IR and ^{1}H NMR spectra for the isolated complex were identical to those of the spirocyclic Meisenheimer complex 92. This suggests that in the solvents acetone and DMSO (the ^{13}C NMR solvent) spirocyclization and loss of methanol are facilitated. In addition to this, an ^{1}H NMR experiment was conducted where the spirocyclic Meisenheimer complex 92 was dissolved in DMSO and one equivalent of methanol was added. The resulting ^{1}H NMR spectrum was identical to that of the 2-methoxy-(2-hydroxyethoxy) Meisenheimer complex 93. The conclusion is that, when the 2-methoxy-(2-hydroxyethoxy) Meisenheimer complex 93 is dissolved in an NMR solvent, it spontaneously cyclizes with the loss of methanol.

The UV spectral behavior is not expected to be a sensitive probe for the structures of the two Meisenheimer complexes, because their maxima are very similar or, in fact, identical. It is likely, however, that the nonspirocyclic complex 93, when dissolved in acetone, is converted to the spirocyclic complex 92; thus the UV spectrum being recorded is that of 92 in any case. In an experiment where the spirocyclic complex 92 was dissolved in acetone and a small amount of methanol was added, there was no change in the UV spectrum.

To confirm this transformation chemically, the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex 93 was treated with one equivalent of potassium thiophenoxide. After purification of the product, the IR and ^{1}H NMR were identical to that of the known spirocyclic Meisenheimer complex 92. To the best of our knowledge, this is the first known set of interconvertible Meisenheimer complexes. (See Fig. 35)

The same 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex 93 was obtained in quantitative yields by treatment of the dinitrolactone 39 or the dinitro methyl ester 40 with excess sodium methoxide at room temperature. However, if the reaction mixtures were heated at reflux and then acidified, the resulting nucleophilic aromatic substitution product, 2-methoxy-3,5-dinitrobenzoic acid (90), could be obtained.

Interconversion of Meisenheimer Complexes 92 and 93

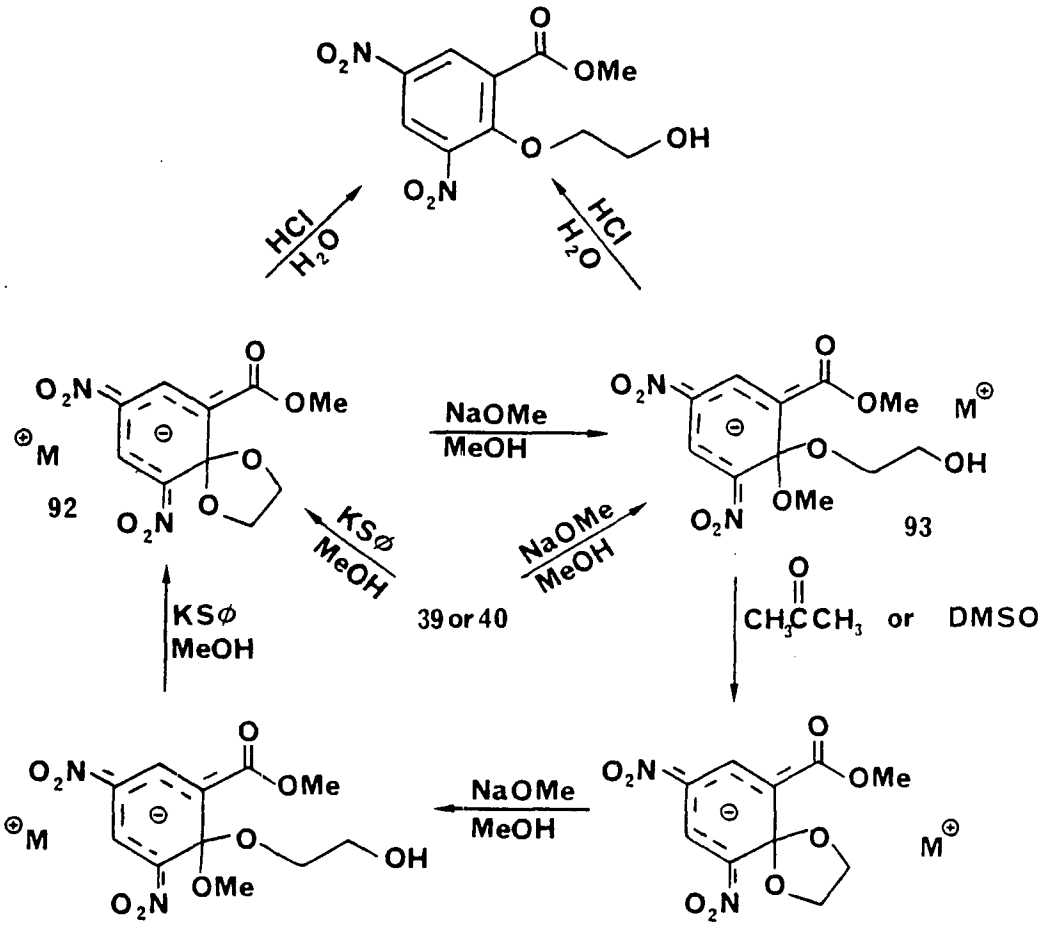
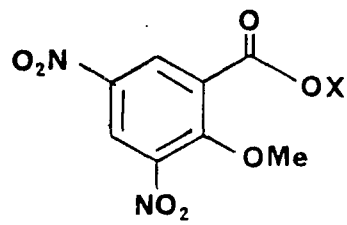


Fig. 35

Careful monitoring of these reactions was undertaken. It was found that when the dinitrolactone 39 or the dinitro methyl ester 40 was heated at reflux in a solution of sodium methoxide, a yellow salt could first be isolated from the reaction mixture. This salt was identified as

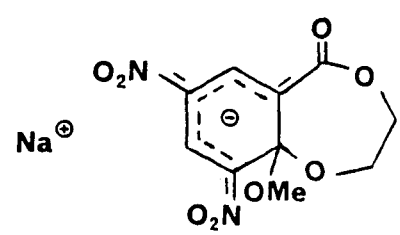
the sodium salt of 2-methoxy-3,5-dinitrobenzoic acid 94. Acidification of the salt afforded the corresponding acid 90.



90 X = H

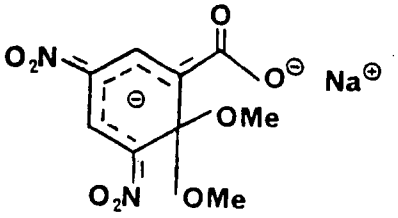
94 X = Na

Concentration of the red solution after the removal of the yellow salt afforded a maroon solid which was tentatively assigned the structure 95, the methoxy lactone Meisenheimer complex. The maroon complex 95 showed UV absorptions typical of a Meisenheimer complex at 386.5 and 471.5 nm. It has not been possible to isolate and characterize it by other means thus far. This maroon solid, when treated with aqueous hydrochloric acid, affords the corresponding nucleophilic aromatic substitution product 90.



95

Bernasconi and coworkers have identified the very similar 1,1-dimethoxy complex 96 by UV studies.[278] This



96

complex showed absorptions at 364 and 488 nm. Therefore, it can be stated with some certainty that the compound isolated in this study is not the complex that Bernasconi has observed by UV spectroscopy. The UV of the maroon complex 95 is more like that of the spirocyclic Meisenheimer complex 92. However, without the aid of other spectroscopic measurements, a definitive assignment for the structure of 95 cannot be made.

A possible explanation to account for these experimental results would be the following. The methoxide ion would attack at either the carbonyl or the aromatic nucleus, first to afford the Meisenheimer complex 93. When the complex 93 is heated in the presence of excess sodium methoxide, ring closure could occur to afford the methoxy lactone 95. Continued heating could cause the opening of the lactone ring with a loss of the β-hydroxyethoxy ester, with formation of the dinitro acid

salt 94. (See Fig. 36) It should be noted that the reactants must be heated at reflux temperature in order to effect nucleophilic aromatic substitution. Treatment of the maroon solid 95 with aqueous acid would lead to the product 90 by re-aromatization and fast hydrolysis of the proposed β-hydroxyethoxy ester.

With the availability of the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex 93, its behavior toward various nucleophiles could be studied. Again, no S_NAr reactions took place with hydroxide, thiophenoxide, methoxide, or ammonium hydroxide unless the reaction mixtures were heated at reflux at least for a brief period of time. If the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex was heated at reflux with the aforementioned nucleophiles, substitution did occur to afford 82, 84, 90, or 61 in quantitative yields. Once again, this type of behavior of a Meisenheimer complex has not been reported in the literature previously.

In both the spirocyclic Meisenheimer complex 92 and the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex 93 the structures resemble that of a ketal. Ketals are not subject to base hydrolysis and an attack at an sp^3 hybridized carbon in an S_N2 attack is not likely. In view of the known stability of ketals in base, the isolation of S_NAr products may be explained in the following manner. The Meisenheimer complexes, in equilibrium with their open rearomatized form(s), undergo S_NAr attack. Such a

sequence of steps is depicted in Figure 33 where thiophenoxide is the nucleophile.

Aqueous acid hydrolysis of the spirocyclic Meisenheimer complex 92 and the "mixed" Meisenheimer complex 93 both afforded the dinitro methyl ester 40, which was a very interesting result. Hydrolysis of the spirocyclic complex 92 was expected to afford the dinitro

Conversion of the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex to 2-methoxy-3,5-dinitrobenzoic Acid, Sodium Salt

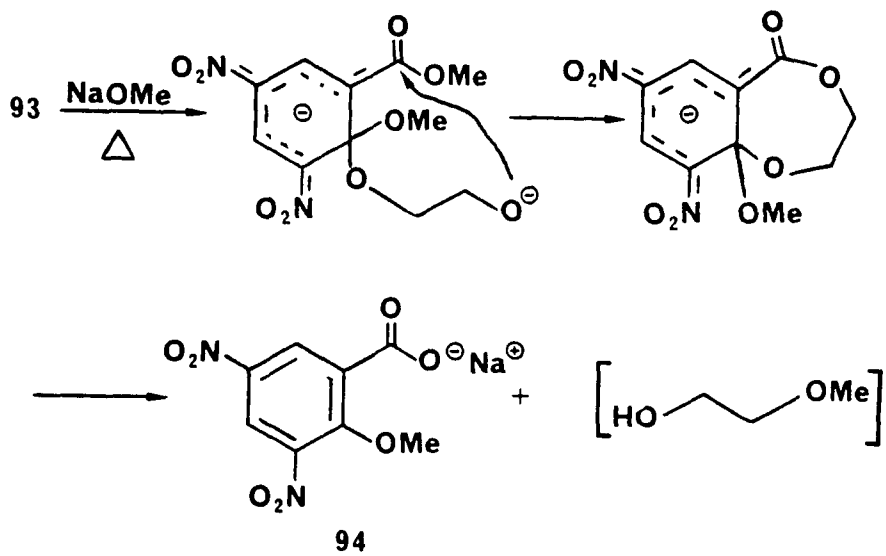
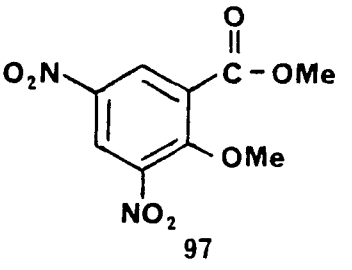


Fig. 36

methyl ester 40, however, the "mixed" complex could have been hydrolyzed to afford two products, either the dinitro methyl ester 40 or 97.



97

Bernasconi has invoked stereoelectronic control to account for observations that spirocyclic Meisenheimer complexes are hydrolyzed more rapidly than the 1,1-dimethoxy Meisenheimer complexes, even though the spirocyclic complexes are thermodynamically favored.

In the present case, there are many possible conformations for the "mixed" complex 93 to adopt. Conformations would be favored where the anomeric effect is minimized and there is a staggered arrangement about the C-O bonds. In conformations A and B these criteria are met; but also there are minimal steric interactions between the ortho substituents and the ether functionalities. Because of steric constraints, it would appear that the methoxy group rather than the β-hydroxyethoxy group would be located "under" the ring, as in A.

Conformations of Meisenheimer Complexes

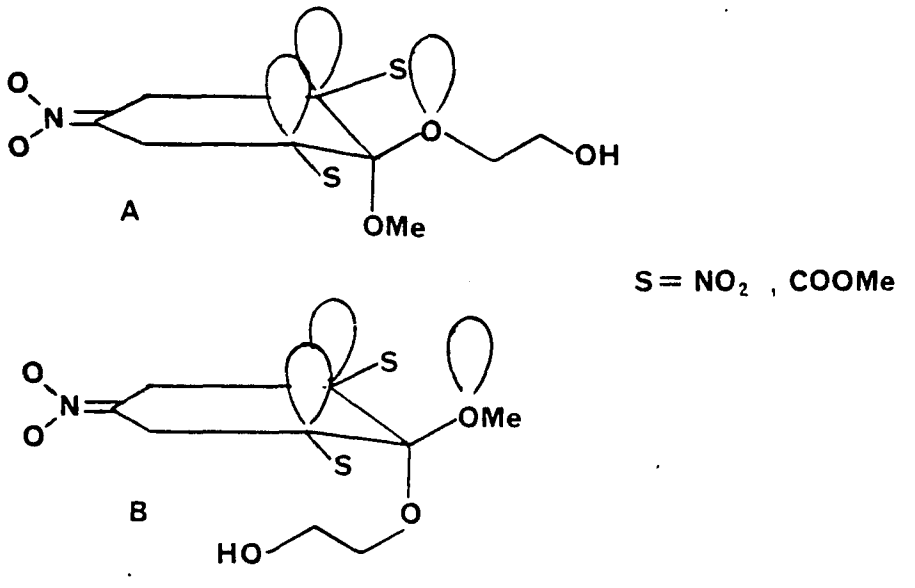


Fig. 37

In order to explain why the methoxy group in the "mixed" complex 93 departs upon hydrolysis in favor of the β-hydroxyethoxy group, stereoelectronic control can be invoked. In conformer A, with the methoxy under the ring, a p orbital on the ether oxygen of the ethoxy side chain can be aligned anti-periplanar to the departing methoxy group, while the p orbitals at the ortho positions are also anti-periplanar to the methoxy group. This is shown in Figure 37.

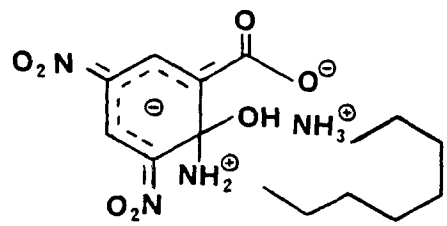
An alternate explanation would be that the mixed Meisenheimer complex 93 first cyclizes to the spirocyclic Meisenheimer complex 92 which is then hydrolyzed. Even if this is the case, stereoelectronic control, as explained

previously, could still account for the final formation of the dinitro methyl ester 40.

Stereoelectronic control can account for the spirocyclization of the 2-(2-hydroxyethoxy) Meisenheimer complex 93 to the spirocyclic Meisenheimer complex 92 in DMSO or acetone. Based on steric considerations, the 2-(2-hydroxyethoxy) functionality would not be favored to lie under the ring. With the methoxy group under the ring, a lone pair of electrons on the ether oxygen of the hydroxyethoxy group would be in an anti-periplanar relationship. Loss of the methoxide ion would generate one equivalent of base, which could then remove the hydroxyl proton of the hydroxyethoxy function. The resultant alkoxide could then attack the aromatic nucleus and form the spirocyclic Meisenheimer complex 92 with the formation of methanol.

The possibility of synthesizing a zwitterionic Meisenheimer complex was envisioned, although this type of complex has not been reported in the literature. A diamine would serve as both a nucleophile and precursor of a cationic site in a zwitterionic Meisenheimer complex. When 1,6-diaminohexane and the dinitrolactone 39 reacted in water, a yellow salt precipitated from solution. Elemental analysis, ^{1}H NMR, ^{13}C NMR, and IR all lend support that the salt is the zwitterionic Meisenheimer complex 98. The ^{1}H NMR shows the typical doublet of doublets and an upfield shift for the cyclohexadienate

protons. The IR spectrum shows a broad OH and ammonium salt stretch, along with the typical C=C stretch at 1600 as well as the shifting of the nitro stretching region to 1530 and 1330 cm^{-1}. ^{13}C NMR shows 6 aliphatic carbons along with the "aromatic" carbons and C=O. The UV spectrum shows one strong absorption at 371 nm in acetone atypical of Meisenheimer complexes; but it is noted that the chromophore is changed with no lone pair on the nitrogen. The added positive charge adjacent to the cyclohexadienate ring may affect the UV absorption substantially. This would be the first zwitterionic Meisenheimer complex ever isolated.



98

To eliminate the possibilities that the compound was not a 2:1 or 1:1 salt of the dinitrosalicylic acid and the amine, UV studies were done to distinguish between these salts and the complex 98. Addition of sodium hydroxide to the dinitrosalicylic acid produced a single absorption at 358 nm. Addition of various amounts of 1,6-diaminohexane also gave an identical absorption at 358 nm. Treatment of

the dinitrosalicylic acid with triethylamine gave a UV absorption at 358 nm. This spectral evidence supports the conclusion that the material isolated 98 is not a simple salt but more likely the zwitterionic Meisenheimer complex as depicted.

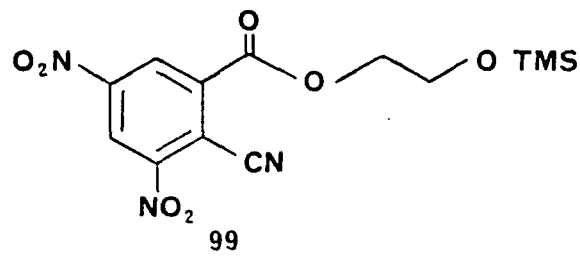
Once again the loss of the β-hydroxyethyl ester was noted. To account for structure 98, the following explanation may be considered. The diamine attacks the aromatic nucleus in an S_NAr fashion with concomitant loss of an ethylene oxide fragment. After this occurs, hydroxide can then attack the aromatic nucleus to generate 98.

Several carbon nucleophiles and thiocyanate were also chosen as reagents to be studied. Although sufficient evidence for S_NAr reactions with these anions is lacking, the results are of interest and provide insight into the broader scope of the interaction of 39 and 40 with nucleophiles.

Cyanide ion was chosen as a carbon nucleophile, even though it is a poor nucleophile for S_NAr reactions, the von Richter Reaction taking place instead.[324] The possibility that the cyanide ion would react was attractive because the product would be a phthalic acid derivative. An additional advantage in using the cyanide ion would be that the proposed β-hydroxyethyl ester might remain intact because cyanide ion would not likely attack an ester or lactone.

Initial experiments with the cyanide ion appeared promising. They were conducted with DMSO, acetone, and even water as reaction solvents and monitored by TLC. If, the organic solvents were dry, no reaction appeared to occur. Upon the addition of a small amount of water, the dinitrolactone 38 was no longer present in the reaction mixture within one hour. Two components were visible by TLC without the use of UV light. The faster moving component was pink, and the slower moving component was orange. Along with these two components, a great deal of tar was also produced with the addition of water. Various aqueous workups were tried in order to isolate the components from the reaction mixtures. Purification of the products was not possible, and no definitive spectral assignments could be made. In other attempts, at lowered temperatures of -78^{o} and -46^{o}, only the dinitrolactone 39 was recovered after the addition of water or diethyl ether. This approach was not pursued any further.

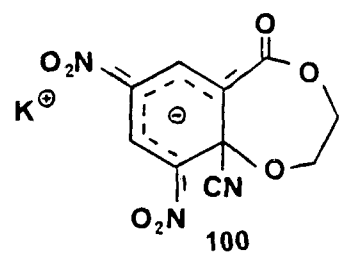
A cyanide reagent was sought that had a built in trapping agent, in the hope that the β-hydroxyethoxy ester could be retained. Trimethylsilyl cyanide (TMSCN) seemed the ideal reagent. It was envisioned that the cyanide would effect a nucleophilic attack on the aromatic nucleus, and the trimethylsilyl moiety would be the trapping agent for the alkoxy group with formation of 99. Several experiments were performed with TMSCN and the dinitrolactone 39 as the substrate. The reaction



99

conditions included adding the TMSCN to the solid dinitrolactone 39 without any solvent, to a solution in THF at room temperature, and to a THF solution at an elevated temperature for one day. TLC analysis of all the reaction mixtures indicated that the dinitrolactone 39 was the sole reaction component. Addition of solid potassium cyanide had no effect on any of the reactions. Addition of solid 18-Cr-6 as a catalyst to enhance the nucleophilicity of the cyanide ion was tried to no avail. When the dinitrolactone 39 was dissolved in DMSO and treated with potassium cyanide and trimethylsilyl chloride for one week, TLC analysis showed a single product but no dinitrolactone. A tan substance was forced out of the mixture by the addition of water. Spectral evidence showed that the compound isolated was not the dinitrolactone 39, but no conclusion as to the identity of the tan material could be drawn. ^{1}H NMR and ^{13}C NMR confirmed that no trimethylsilyl group was present in the compound. Further investigation of the compound was not undertaken.

In all of the reaction mixtures from the dinitrolactone 39 and potassium cyanide a purple-red color was observed. This suggested that a Meisenheimer complex might have been present. The UV spectrum of a solution of dinitrolactone 39 in acetone did not show the characteristics of a Meisenheimer complex. Addition of potassium cyanide caused the solution to become purple, and two new UV absorptions were noted at 374 and 505 nm. These absorptions are typical of Meisenheimer complexes. Addition of dry diethyl ether, in attempts to force out the Meisenheimer complex, always caused the dinitrolactone 39 to precipitate. If the Meisenheimer complex 100 is being formed, as suggested by the intense color and the UV spectrum, it is reverting to 39 upon the addition of ether. This instability was not unexpected, for it has been noted in earlier literature that experiments involving an apparent cyanide Meisenheimer complex are often difficult to reproduce.[325, 325] To date, no cyanide Meisenheimer complexes have been isolated in solid form.



100

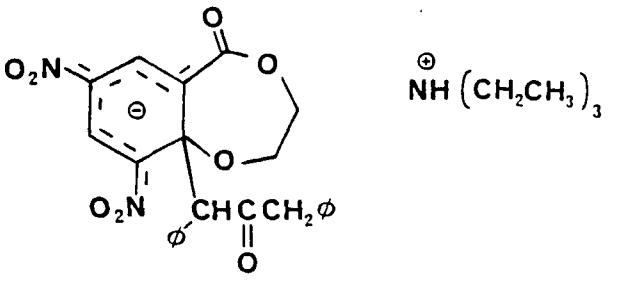
The use of enolates as carbon nucleophiles to effect S_NAr reactions was explored. The enolate of ethyl cyanoacetate, generated from sodium hydride in THF was inert toward the dinitrolactone 39. This was probably due to the poor solubility of the dinitrolactone 39 in THF.

In another approach, ethyl cyanoacetate was added to the dimsyl anion in DMSO.[327, 328] When the dinitrolactone was added to the mixture, a reaction appeared to occur according to TLC analysis. Aqueous workup with dilute acid or ammonium chloride afforded a tar which could not be purified. These experiments did show some promise. The reaction mixture had an intense purple color after the dinitrolactone 39 and the enolate had been mixed together. This may indicate the formation of a Meisenheimer complex.

Acetone, dimethyl malonate, and 1,3-diphenyl propanone were chosen as possible alternative enolate nucleophiles. Several experiments were attempted with acetone where triethylamine was used as a solvent/base for the generation of the enolate in the presence of the dinitrolactone 39. It was found that the dinitrolactone 39 was unchanged under these conditions, where it failed to dissolve. After the minimum amount of DMSO was added to solubilize the dinitrolactone 39, an intense purple color was noted with all three enolates. The UV spectrum in acetone (methanol destroyed the complex) showed the appearance of two absorptions at 373 and 478 nm for the

complex formed from the interaction of the enolate of 1,3-diphenyl propanone and dinitrolactone 39. A possible structure for this complex would be 101.

Several attempts to isolate any of the complexes were futile. Diethyl ether, toluene, and cyclohexane were used to force out the ammonium salts of the Meisenheimer complexes. In each case, only the dinitrolactone 39 was isolated. Further investigation is needed in this area to develop the best choice of solvent and amine base for stabilization and possible isolation of the complexes.



101

When the enolates from dimethyl malonate or 1,3-diphenylpropanone were generated from sodium methoxide in methanol, an unexpected result occurred. Coloration of the reaction mixture suggested nucleophilic attack was taking place. Isolation of the product in quantitative yield after 1 h, however, showed the material to be identical to the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex 93. An important point to note is that this reaction outlined above took approximately 1 h to go to completion. The same reaction with dinitrolactone 39 in a solution of sodium

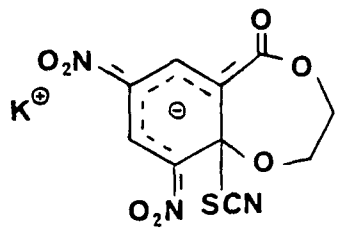
methoxide/methanol is instantaneous. The fact that the enolates fail to attack 39, which is then slowly converted by methoxide to the Meisenheimer complex, may reflect the unfavorable steric bulk of the enolate nucleophiles. In spite of the low equilibrium concentration of methoxide, it eventually attacks the aromatic nucleus to give the product 93.

A series of experiments were conducted where thiocyanate ion was examined as the nucleophile. The incorporation of this group was extremely attractive because of the known biological activities of nitrated aromatic thiocyanates.[330-332] Previous syntheses of picryl thiocyanate and 2-thiocyanato-3,5-dinitrobenzoic acid, methyl ester have been achieved by using nucleophilic aromatic substitution reactions, with methanol, acetone, DMF, and DMSO as solvents.[330, 333, 334] The reaction rates are accelerated greatly in acetone, DMF, and DSMO by comparison to alcohols.[335] Although thiocyanate is an ambitentate nucleophile, it typically reacts as a sulfur nucleophile in S_NAr reactions.[305, 336, 337]

Treatment of the dinitrolactone 39 with potassium thiocyanate in ethanol or ammonium thiocyanate in THF under various conditions led only to recovery of the starting material. However, when the dinitrolactone 39 was treated in dry DMSO at 110° with potassium thiocyanate, a yellow salt was obtained in quantitative

yields. If the DMSO was wet, an unidentifiable product was obtained. No reaction occurred if the reaction temperature was maintained below 85°.

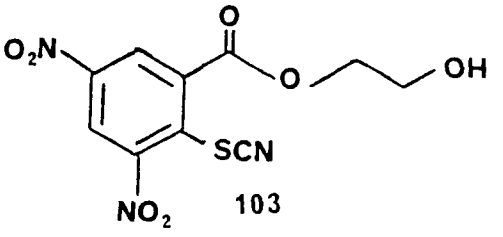
On the basis of analogy with other nucleophiles, the salt might be assigned the structure 102 as a Meisenheimer intermediate. IR and ^{1}H NMR evidence support this



102

structure, but from the ^{13}C NMR it was clear that one of the aliphatic carbons was greatly shielded, with a chemical shift of 32.45 ppm. This is in contrast with other compounds already described that show the $-(OCH_2CH_2O)-$ methylene carbons to have chemical shift values between 70 and 60 ppm. UV spectra in several solvents did not show the absorptions typical of Meisenheimer complexes, but rather one like that of a dinitrophenolic salt with an absorption at 365 nm. A survey of the literature showed that 3,5-dinitrosalicylic acid esters all have strong UV absorptions between 360-380 nm, as do their corresponding salts.[338]

Acidification of the salt afforded a new compound that was fully characterized. If the Meisenheimer complex were 102, then this acidification product would be expected to have structure 103. Analysis of the spectral data, however supported compound 104 as the most likely



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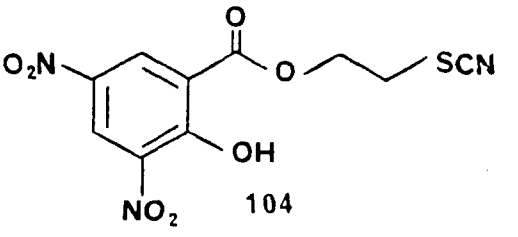
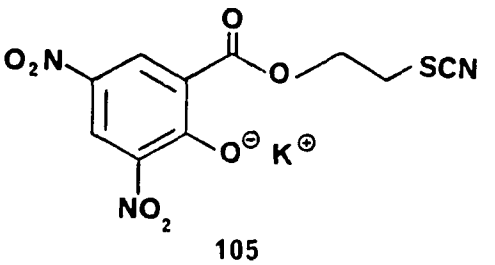


104

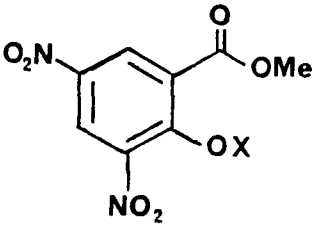
structure. ^{13}C NMR showed a methylene carbon at 32.2 ppm. This chemical shift was more like that of a carbon to a thiocyanate.[339, 340] The UV of this compound was also consistent with structure 104. It showed a characteristic absorption of a 2,4-dinitrophenol at 365 nm, in contrast to 2,4-dinitrophenyl thiocyanate, with a maximum at 257 nm.

Confirmation of the structure of the thiocyanatoethyl ester 104 came from acid or base hydrolysis of 104, which afforded 3,5-dinitrosalicylic acid 82. Therefore, the conclusion was drawn that the salt first isolated was not a Meisenheimer complex but actually the phenolic salt 105.



105

Compounds 97 and 106 were synthesized in order to compare their UV spectra to the UV spectrum of the dinitrolactone 39. It was found, not unexpectedly, that the dinitrolactone 39 and the 2-methoxy ether 97 had similar UV absorption patterns with maxima at 270 nm. This was in comparison to the phenolic compounds 104, 105, and 106 which all had characteristic λ max at approximately 360 nm. (See Table VI) This comparison was done to demonstrate that 104 resembles typical dinitrosalicylic esters.



X = Me 97
X = H 106

Table VI. UV of Dinitrobenzote Esters

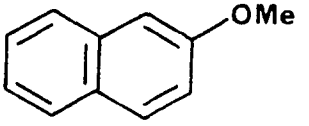
Compound No.	Wavelength 1	Wavelength 2
39	215 (17,750)	282 (9600)
40	213 (21,250)	272 (11,200)
97	213 (20,100)	269 (8165)
104	281.0 (4600)	358.5 (11,200)
105	265 (16,400)	365 (16,500)
106	217 (10,200)	363 (16,130)

It appears that the thiocyanate anion in DMSO is acting as a nucleophile in an S_N2 displacement reaction rather than an S_NAr displacement. This may be attributed to an unfavorable attack of the thiocyanate at the aromatic nucleus, in spite of the linear nature of the nucleophile.

As an indication of the effect solvent had upon the reaction, it should be mentioned that treatment of the dinitrolactone 39 or dinitro methyl ester 40 with potassium thiocyanate in refluxing ethanol or acetone afforded only the starting material. Yet these solvents have commonly been used for the preparation of aromatic thiocyanates.[330, 335] DMSO, being an aprotic solvent, is enhancing the nucleophilicity of thiocyanate.

Because thiocyanate is not known to be an agent for cleavage of ethers, a series of compounds were examined for possible similar ether cleavage by thiocyanate ion.[341] These compounds included the dinitro methyl ester 40, 5-

bromoamide 46, 2-methoxy-3,5-dinitrobenzoic acid, 2-methoxynaphthalene 107, 2-nitroanisole 108, 4-nitroanisole 109, 2,4-dinitroanisole 110, 1,2-(methylenedioxy)-4-nitrobenzene 111, methyl ester 97, and p-methoxyacetophenone 112.



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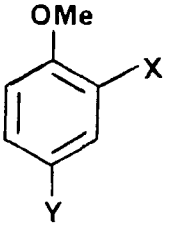
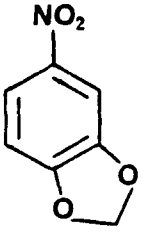


$X = NO_2$	$Y = H$	108
$X = H$	$Y = NO_2$	109
$X = Y = NO_2$		110



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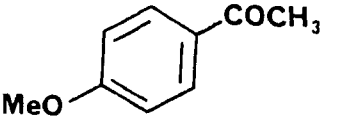


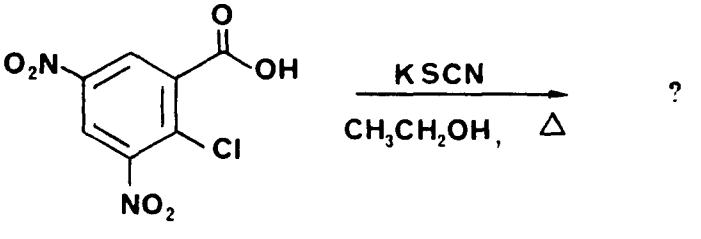
112

The substrate was placed in dry DMSO with 4 equivalents of potassium thiocyanate. The solution was heated at 110° for 1.5 h, then poured while hot into ice/water, and the material was isolated. Only the compounds 39, 40, 90, 97, and 111 showed loss of an alkyl group instead of nucleophilic aromatic substitution. The rest of the compounds were recovered in quantitative

yields. No reaction(s) was observed to occur with any of these compounds. All of the cleavage products isolated were known compounds and were easily identified by IR, ^1H NMR, or mixture melting point methods.

From these observations, it appears that the cleavage of aromatic ethers by thiocyanate is not a general reaction. Aromatic ethers that have two nitro groups on the aromatic nucleus do undergo ether cleavage with thiocyanate ion in dry DMSO. The broader scope of this conversion has yet to be explored.

The ineffectiveness of thiocyanate in S_NAr reactions was apparent in the case of 80, when it was treated with potassium thiocyanate in ethanol/water. Although it has not been identified, a solid material was obtained that was clearly not that of aromatic subsitution. It reacted like a salt and was readily soluble in water.



80

Acidification of the salt resulted in another unidentifiable compound which, however, lacked the thiocyanate group.

SUGGESTIONS FOR FURTHER WORK

Several avenues of approach remain to be pursued from the first part of this investigation. The major emphasis of this research has centered on the dinitrolactone 39 and the dinitro methyl ester 40. With the preparation of these compounds well established, the focus of future research should be directed toward varying the substituents on the aromatic nucleus. This could be accomplished by Sandmeyer reactions on the diamino compounds available by reduction of the nitro groups.[342] This methodology could then be extended to include the mono substituted esters and lactones after viable methods of preparation are developed. Ring closure investigations could be performed to observe what effect(s) the various substituents would have on lactonization.

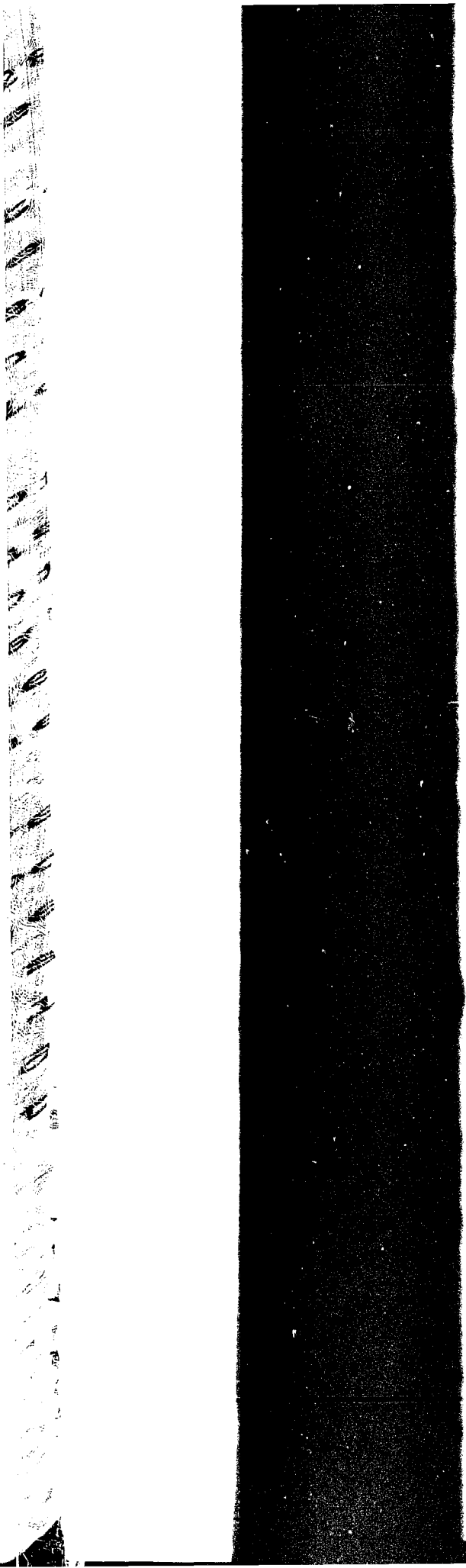
The chemistry developed for compounds derived from 26 might be applied to 2-(11-hydroxy-3,6,9-trioxaundecyloxy)-benzoic acid, methyl ester. Purification and derivatization of this ester may be accomplished in much the same manner. Ring closure reactions and the effect of substitutents in the polyoxygenated systems could thus be explored.

Initial experiments into the exploration of ring-chain tautomerism with nitrile functionality appear

promising. With the methods of preparation for several aromatic substituted substrates established, studies in this area may be productive. A study of the substituted 2-(2-hydroxyethoxy) nitriles would be interesting because the ring tautomer would be an imine which could be hydrolyzed to the corresponding lactone or "trapped" in various standard ways. Reduction of the corresponding acids or lactones to aldehydes by known procedures may lead to compounds which exhibit ring-chain tautomerism by forming lactols.[343-345]

Continued work in the area of nuclophilic aromatic substitution and Meisenheimer complexes appears exciting. The possibility of subjecting the dinitrolactone 39 or the dinitro methyl ester 40 to the attack by carbon nucleophiles may lead into very interesting chemistry. The use of carbon nucleophiles could eventually lead into new heterocyclic systems. Because of the ease of preparation of the spirocyclic Meisenheimer complex 92 and the 2-methoxy-2-(2-hydroxyethoxy) Meisenheimer complex 93, kinetic studies could be performed to determine formation and stability constants.

The scope of sulfur nucleophiles, especially thiosulfate, should be examined carefully in S_NAr reactions with 39 or 40.[305, 335] Changing the solvent system to polar aprotic media may cause a dramatic effect on what occurs during the reaction process. A long range



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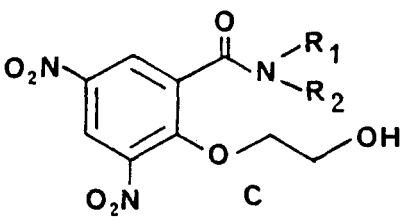
goal would be the preparation of aromatic nuclei containing chiral sulfur groups.

One very interesting area of work would be to continue with the preparation of zwitterionic Meisenheimer complexes. A series of such compounds could be prepared where diamines would be used. With the isolation of the complexes, ^{1}H NMR, ^{13}C NMR, and UV-Vis correlations could be established.

An important study would be to subject a series of dinitroamides with the general structure C to various nucleophiles. This would include a broad array of nucleophilic reagents such as the respective amines, oxygen, carbon, and sulfur compounds. In this way, the effect of amide substitutuion may be studied to examine what effect this has on S_NAr reactions.

The use of the thiocyanate ion in DMSO as a selective demethylating agent requires further study. This method thus far appears to be of practical use because the conditions are mild and the ester functionality remains unchanged. Activated aromatic compounds with methyl ethers should be examined. The compounds studied should include a wide variety of functionality to examine what side reactions may or may not be occurring.



C

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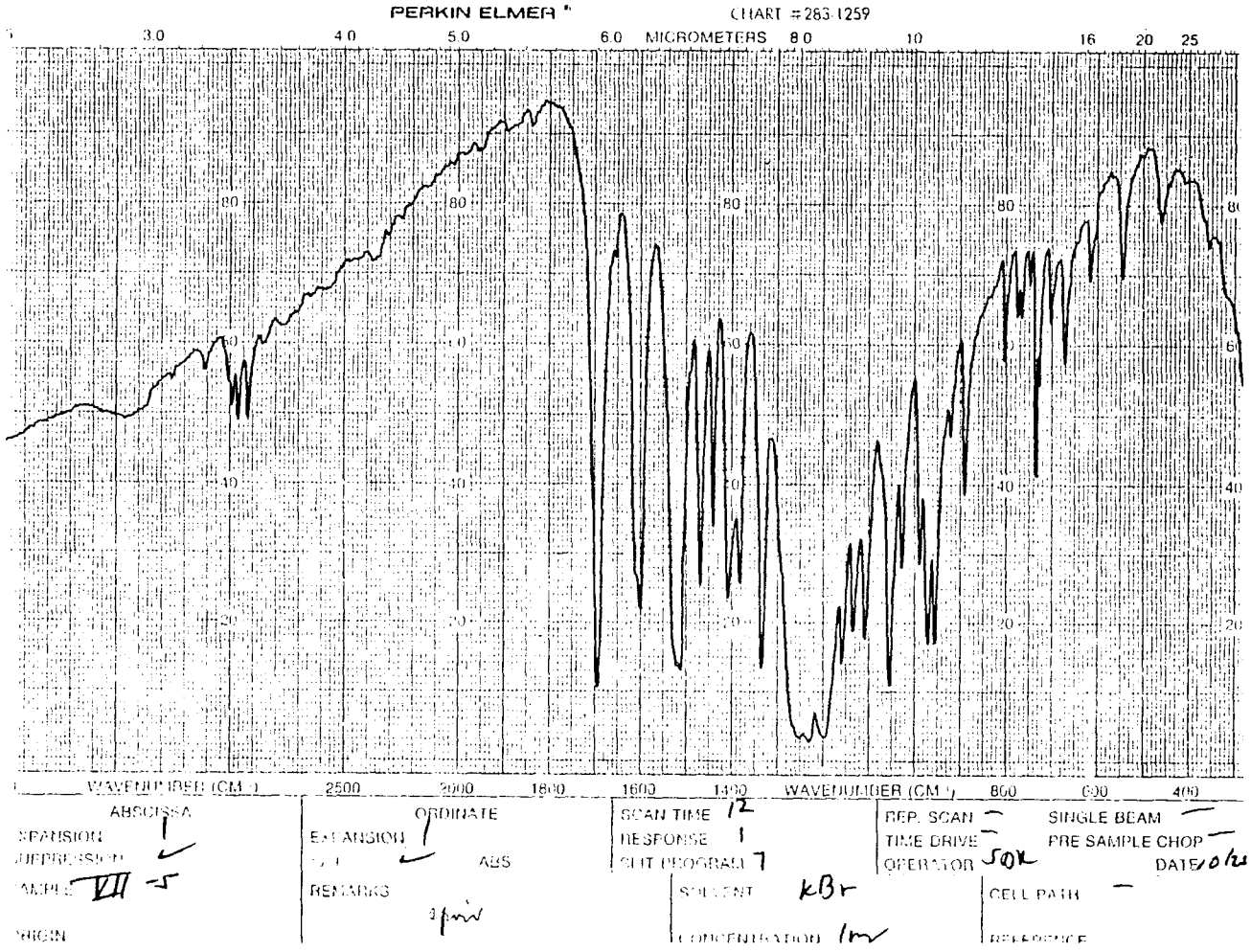
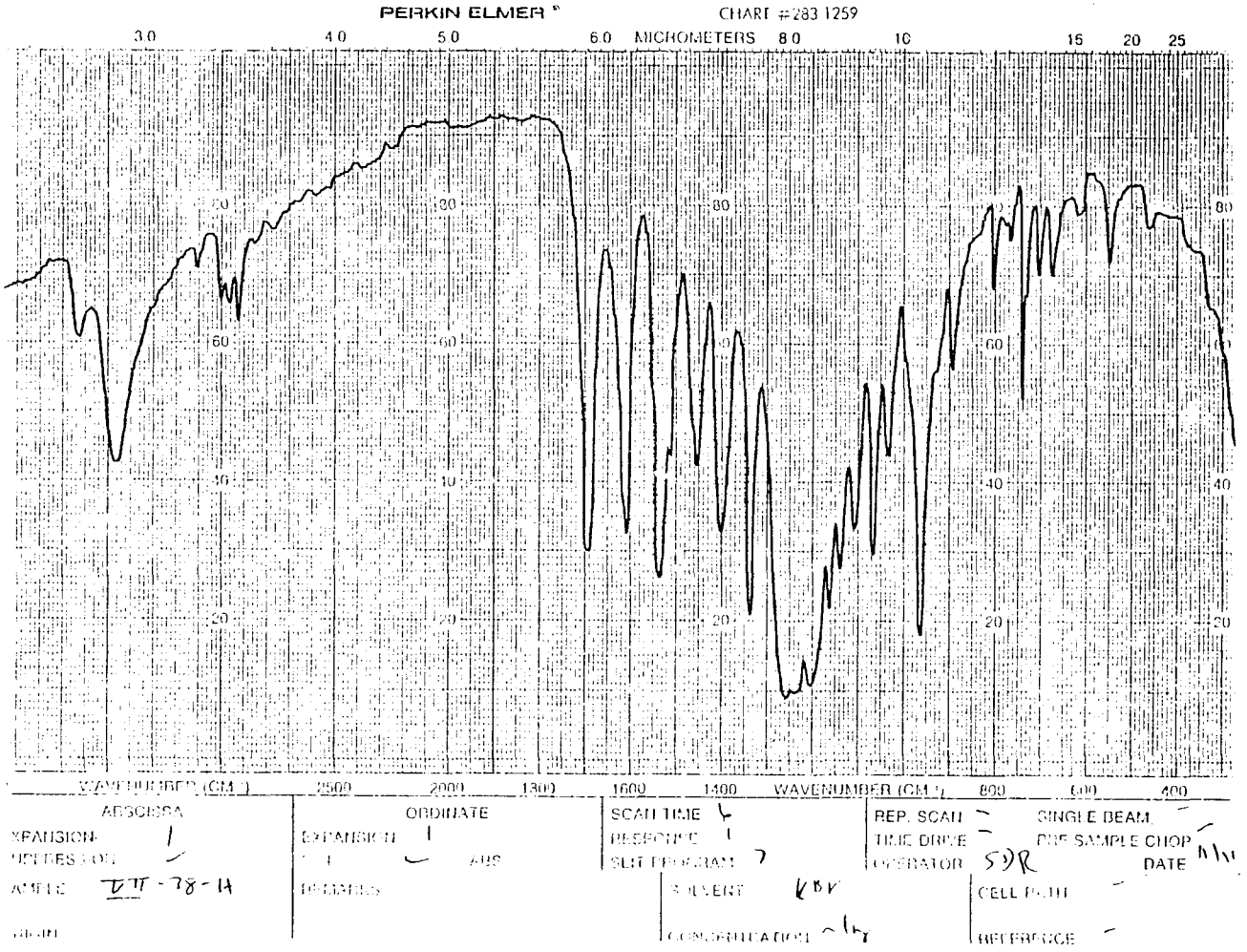
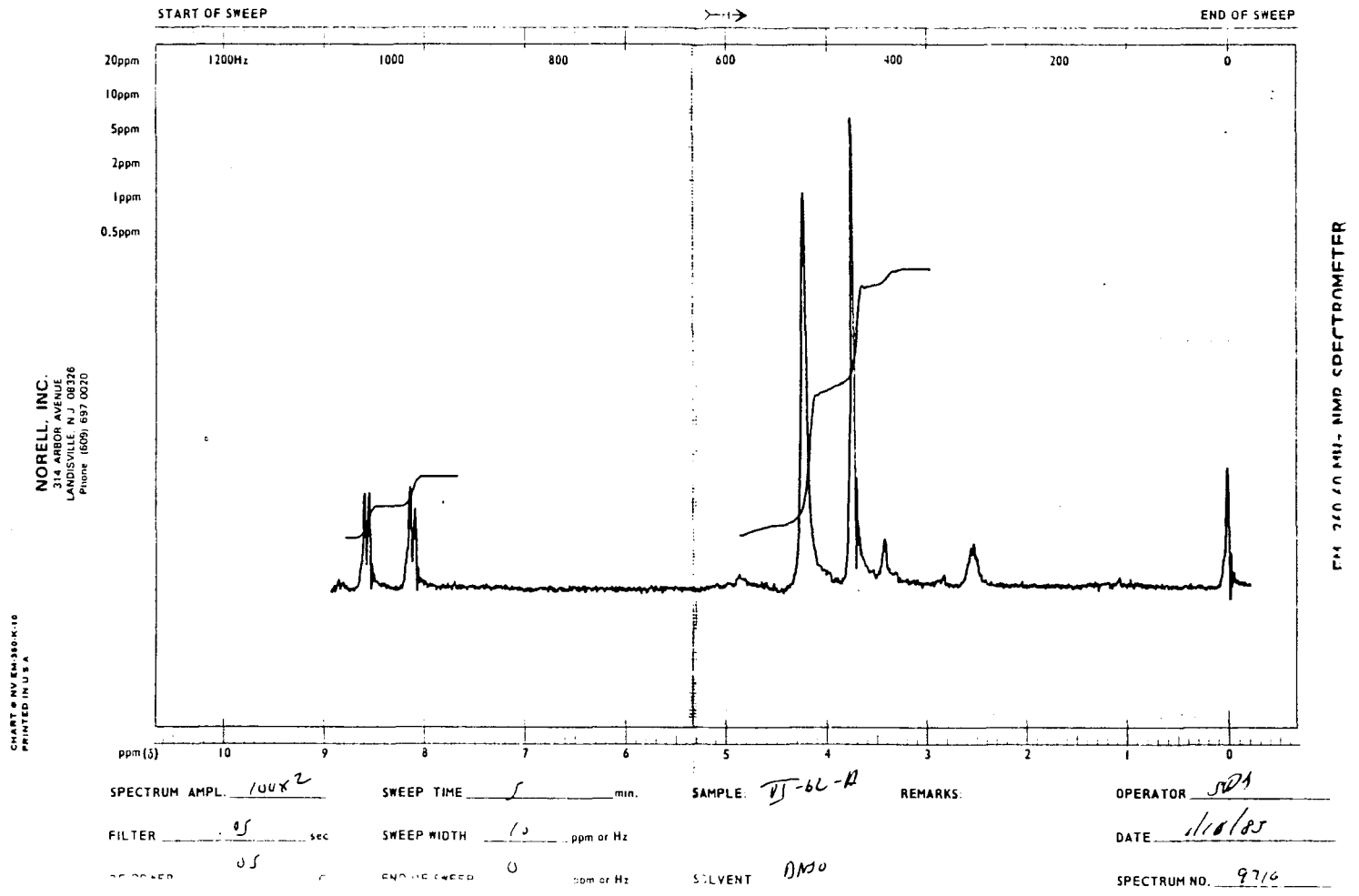
APPENDIX



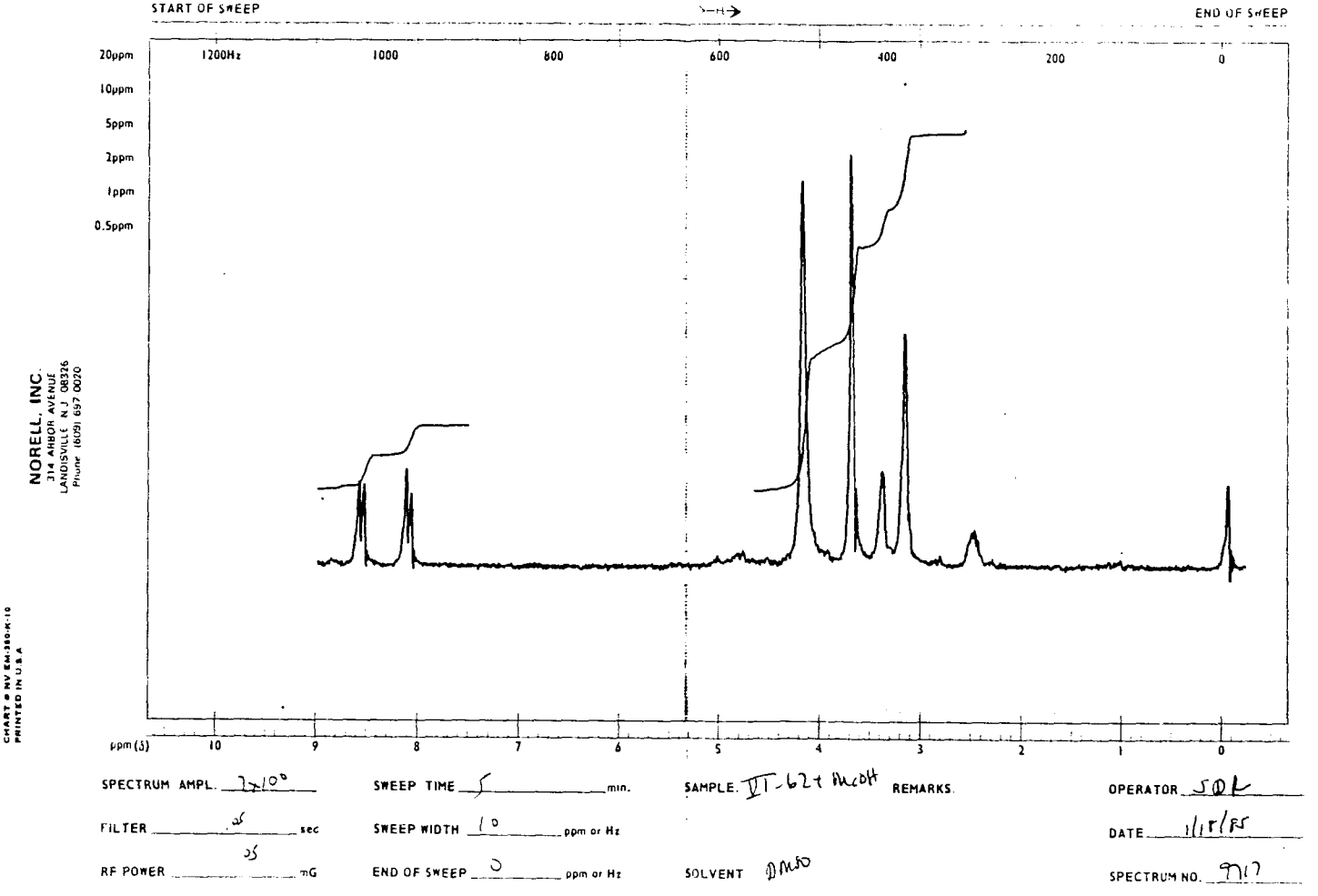
IR of Spirocyclic Meisenheimer Complex 92.



IR of 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex 93.

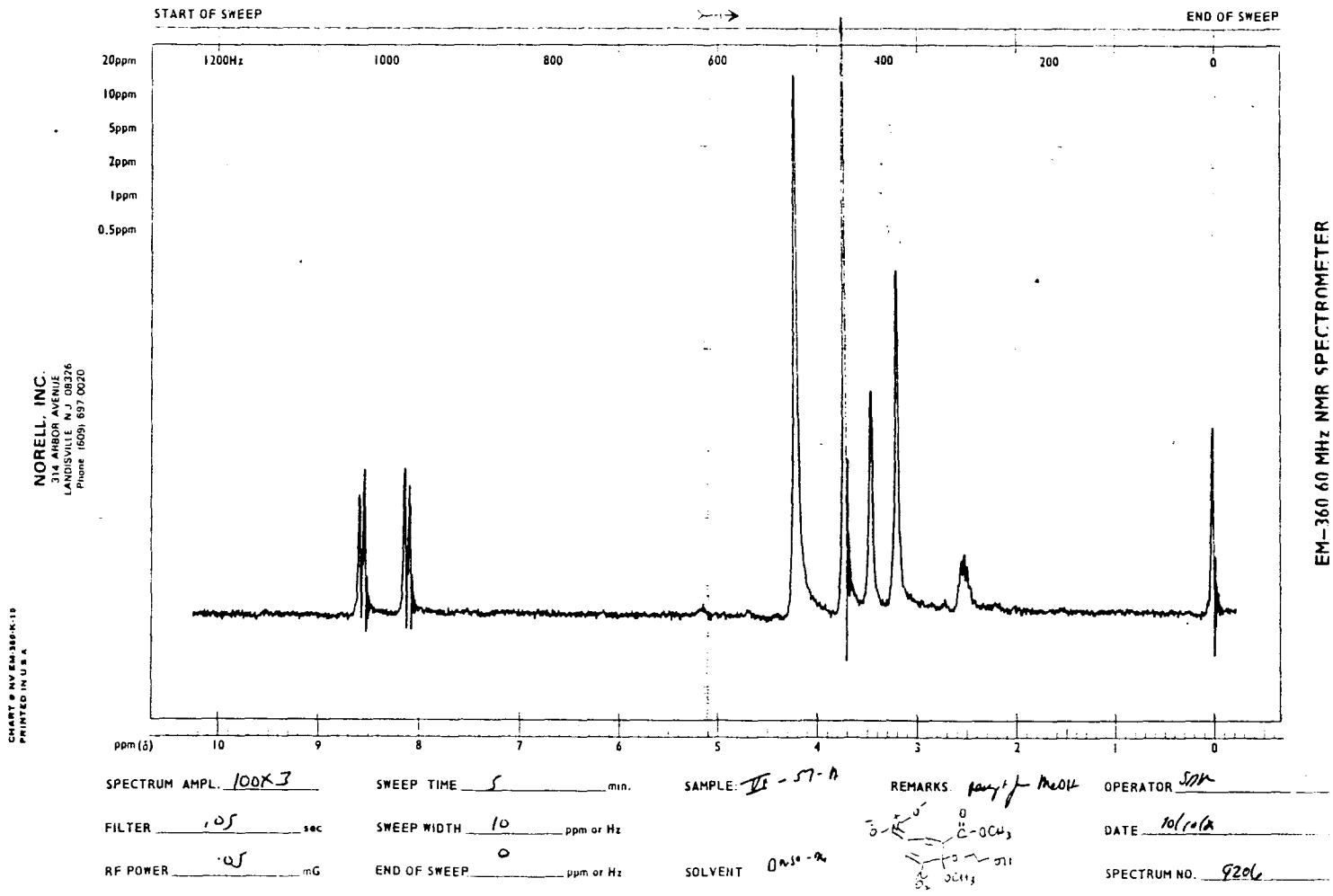


^{1}H NMR of Spirocyclic Meisenheimer Complex 92 in DMSO.

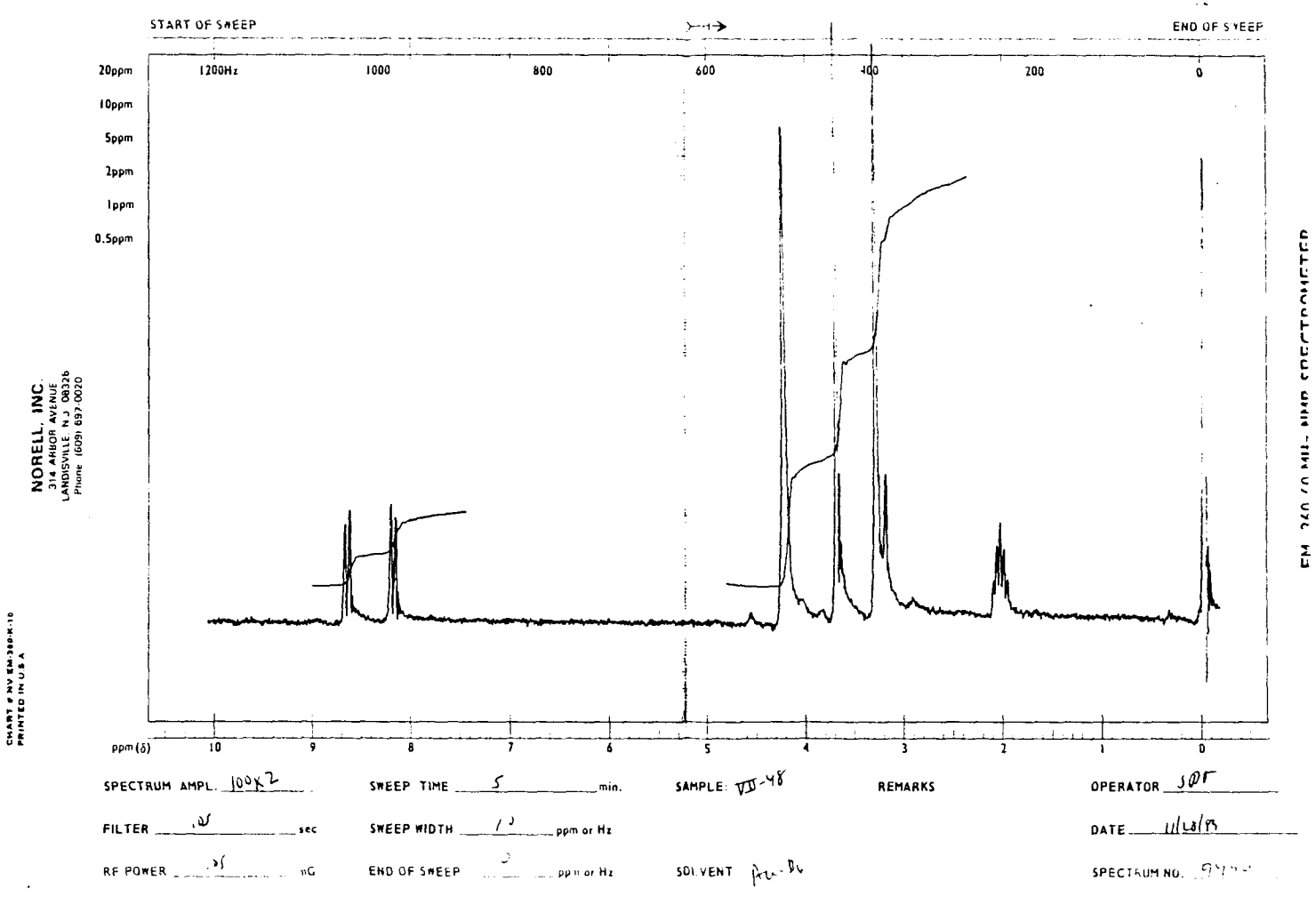


^{1}H NMR of Spirocyclic Meisenheimer Complex 92 in DMSO

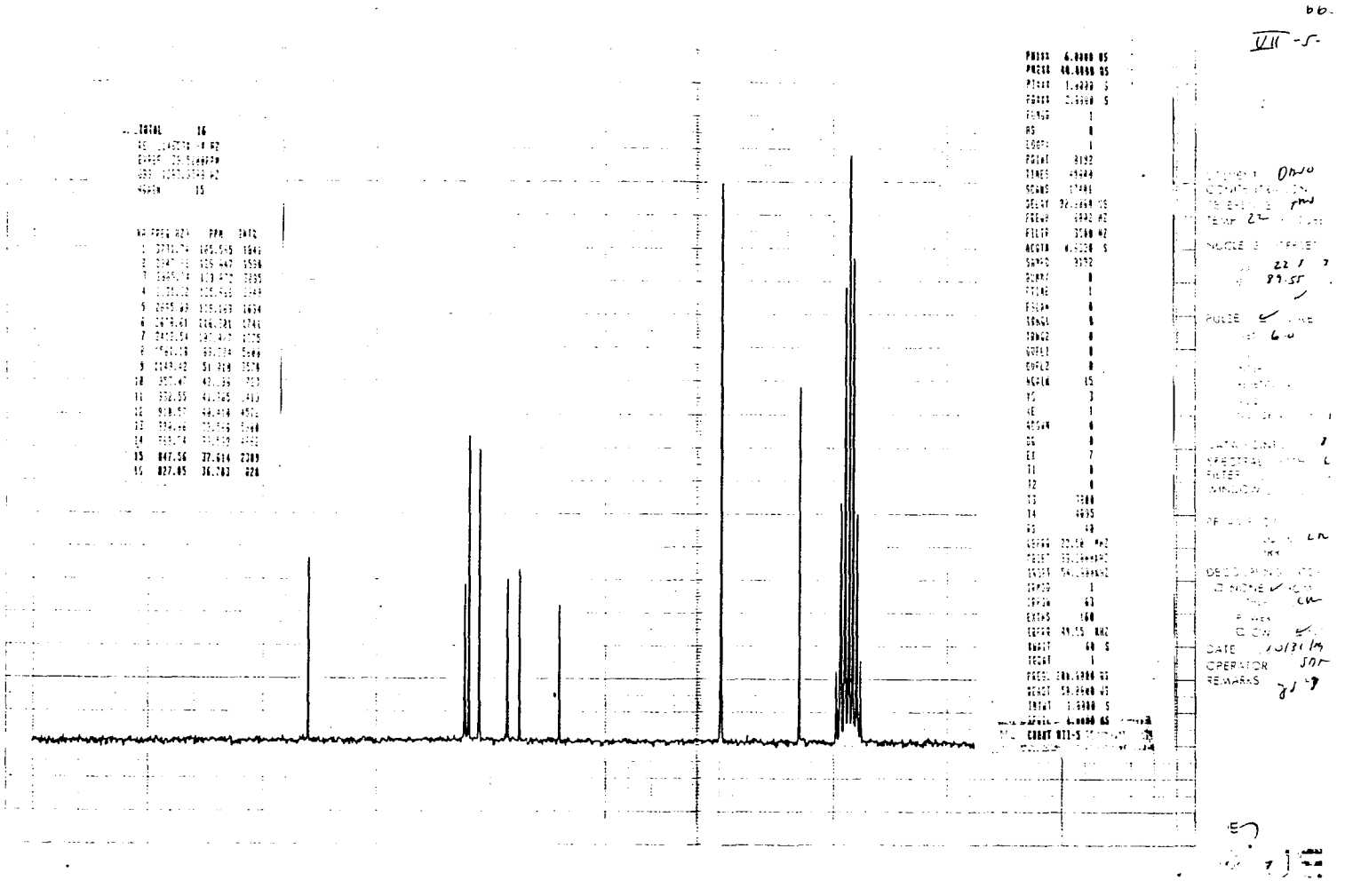
+ One Equivalent of Absolute Methanol.



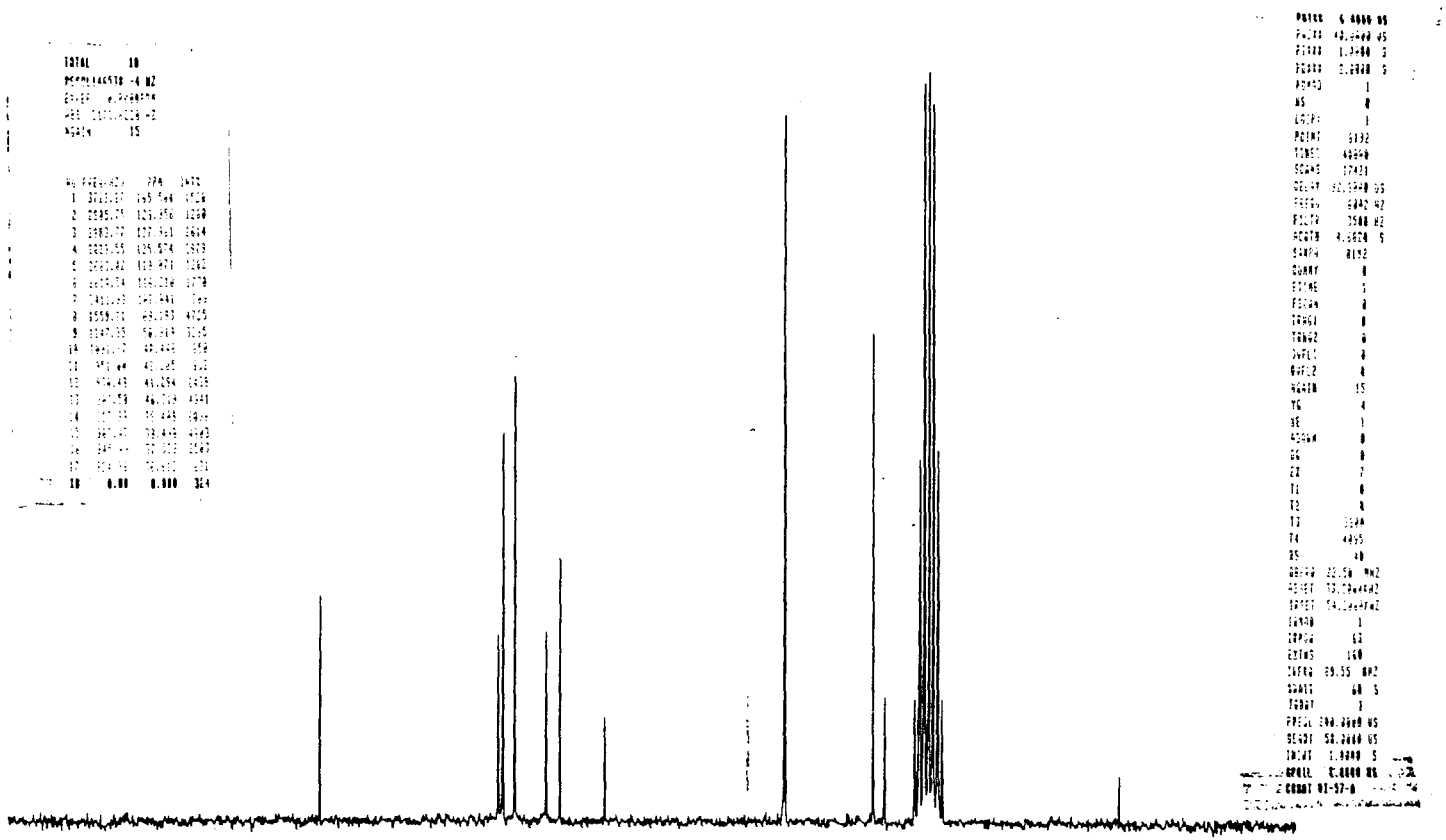
^{1}H NMR of 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex 93 in DMSO.



^{1}H NMR of 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex 93 in Acetone.



^{13}C NMR of Spirocyclic Meisenheimer Complex 92 in DMSO.

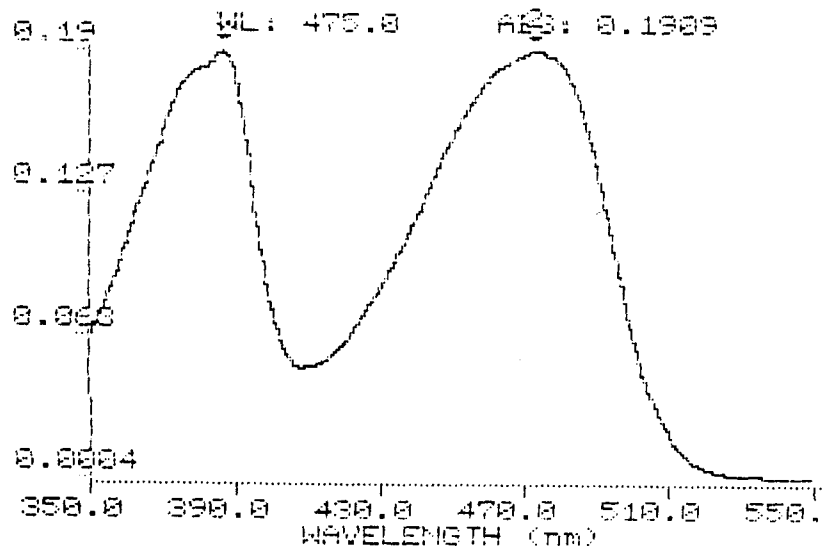


^{13}C NMR of 2-Methoxy-2-(2-hydroxyethoxy) Meisenheimer Complex 93 in DMSO.

PEAK	WAVELENGTH	ABSORBANCE
1	388.0	0.1907
2	475.0	0.1909

SPECTRUM ID #: 1250
SPIROCYCLIC MEISENHEIMER SCAN 1

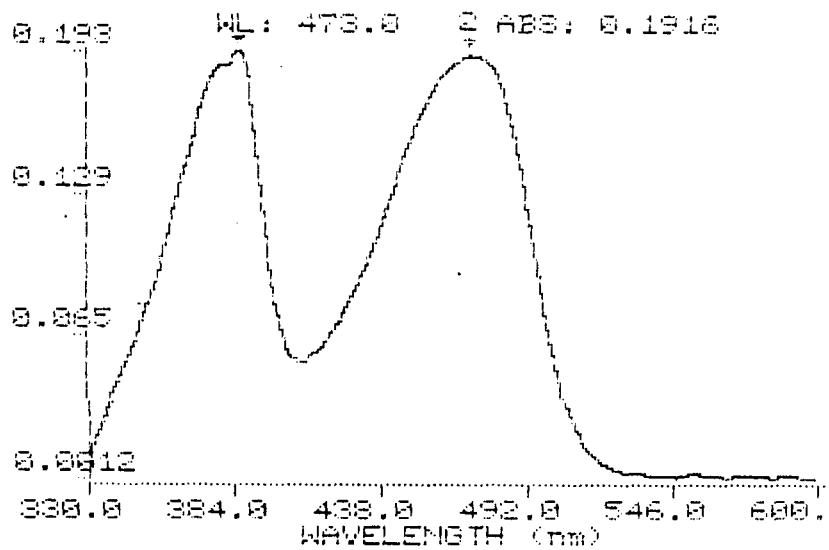
SCAN RATE	(NM/SEC):	2.00
SPECTRAL BAND WIDTH	(NM):	1.00
EFFECTIVE PERIOD	(SEC):	0.5



UV Spectrum of Spirocyclic Meisenheimer Complex 92 in Acetone.

SPECTRUM ID #: 1252
SPIROCYCLE 3.5 ML + 40 ML MEOH SCAN 1

SCAN RATE	(NM/SEC):	2.00
SPECTRAL BAND WIDTH	(NM):	1.00
EFFECTIVE PERIOD	(SEC):	0.5



PEAK	WAVELENGTH	ABSORBANCE
1	387.5	0.1933
2	473.0	0.1916

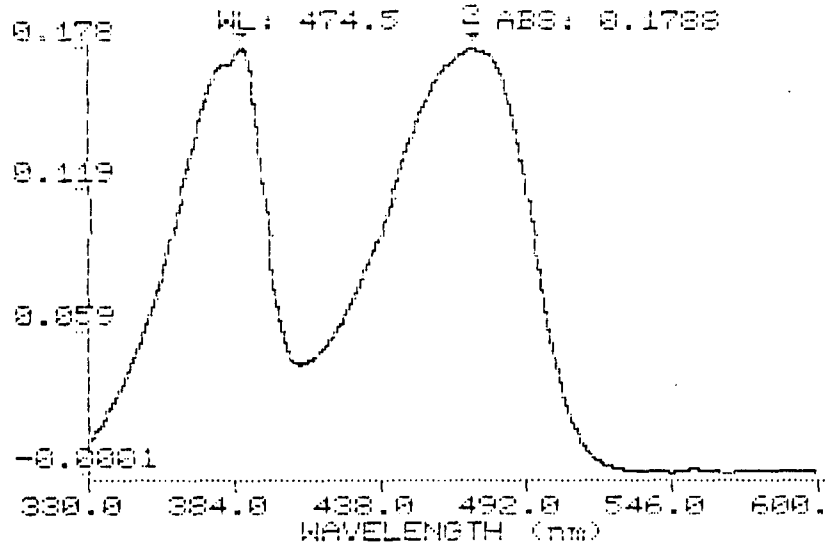
UV Spectrum of Spirocyclic Meisenheimer Complex

92 in Acetone + 40 of Absolute Methanol.

PEAK	WAVELENGTH	ABSORBANCE
1	388.0	0.1785
2	474.5	0.1788

SPECTRUM ID #: 1251
2-METHOXY-2-HYDROXYETHOXY MEISENH SCAN 1

SCAN RATE	(NM/SEC):	2.00
SPECTRAL BAND WIDTH	(NM):	1.00
EFFECTIVE PERIOD	(SEC):	0.5



UV Spectrum of 2-Methoxy-2-(2-hydroxyethoxy)

Meisenheimer Complex in Acetone.